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ABOUT COVER

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META-ANALYSIS

Selection of first-line systemic therapies for advanced hepatocellular carcinoma: A network meta-analysis of randomized controlled trials

Yue Han, Wei-Hua Zhi, Fei Xu, Chen-Bo Zhang, Xiao-Qian Huang, Jian-Feng Luo

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Abstract

BACKGROUND

The majority of clinical trials of first-line systemic treatments for hepatocellular carcinoma (HCC) used placebo or sorafenib as comparators, and there are limited data providing a cross comparison of treatments in this setting, especially for newly-approved immune checkpoint inhibitor and vascular endothelial growth factor inhibitor combination treatments.

AIM

To systematically review and compare response rates, survival outcomes, and safety of first-line systemic therapies for advanced hepatocellular carcinoma.

METHODS

We searched PubMed, Science Direct, the Cochrane Database, Excerpta Medica Database, and abstracts from the American Society of Clinical Oncology 2020 annual congress. Eligible studies were randomized controlled trials of systemic therapy enrolling adults with advanced/unresectable HCC. Risk of bias was assessed with the Cochrane risk of bias tool for randomized controlled trials. A network meta-analysis was used to synthesize data and perform direct and indirect comparisons between treatments. *P* value, a frequentist analog to the surface under the cumulative ranking curve, was used to rank treatments.

RESULTS

In total, 1398 articles were screened and 27 included. Treatments compared were atezolizumab plus bevacizumab, brivanib, donafenib, dovitinib, FOLFOX4, lenvatinib, linifanib, nintedanib, nivolumab, sorafenib, sunitinib, vandetanib, 11 sorafenib combination therapies, and three other combination therapies. For

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overall response rate, lenvatinib ranked 1/19, followed by atezolizumab plus bevacizumab and nivolumab. For progression-free survival (PFS), atezolizumab + bevacizumab was ranked 1/15, followed by lenvatinib. With the exception of atezolizumab + bevacizumab [hazard ratios $(HR)_{PFS}$ = 0.90; 95% confidence interval (CI): 0.64-1.25], the estimated HRs for PFS for all included treatments *vs* lenvatinib were > 1; however, the associated 95%CI passed through unity for bevacizumab plus erlotinib, linifanib, and FOLFOX4. For overall survival, atezolizumab plus bevacizumab was ranked 1/25, followed by vandetanib 100 mg/d and donafinib, with lenvatinib ranked 6/25. Atezolizumab + bevacizumab was associated with a lower risk of death *vs* lenvatinib (HR_{os} = 0.63; 95%CI: 0.44-0.89), while the HR for overall survival for most other treatments *vs* lenvatinib had associated 95%CIs that passed through unity. Vandetanib 300 mg/d and 100 mg/d were ranked 1/13 and 2/13, respectively, for the lowest incidence of treatment terminations due to adverse events, followed by sorafenib (5/13), lenvatinib (10/13), and atezolizumab + bevacizumab (13/13).

CONCLUSION

There is not one single first-line treatment for advanced HCC associated with superior outcomes across all outcome measurements. Therefore, first-line systemic treatment should be selected based on individualized treatment goals.

Key Words: Hepatocellular carcinoma; Systemic therapy; Meta-analysis; Lenvatinib; First-line; Immune therapy

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Core Tip: The present network meta-analysis is the first to compare data from randomized trials of all first-line systemic therapies for hepatocellular carcinoma including chemotherapy, targeted drugs, immunotherapy, and combination therapies. Furthermore, the analysis represents a comprehensive cross comparison of outcomes, including tumor response rates, survival, and safety and included a sub-analysis in patients with hepatitis B virus infection. Our results showed that atezolizumab plus bevacizumab was ranked first for progression-free survival and overall survival but also had the highest rate of discontinuations due to adverse events. Lenvatinib ranked first for overall response rate and second for progression-free survival.

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INTRODUCTION

Liver cancer is the sixth most common cancer globally, accounting for 4.7% of all new cancer cases in 2018, and represents the third most common cause of cancer-related death worldwide behind lung and colorectal cancer[1]. Of the primary liver cancers, hepatocellular carcinoma (HCC) is the most prevalent histological subtype and accounts for 80%-85% of cases[2]. Surgical resection and liver transplant are associated with the best survival outcomes for patients with HCC, and are potentially curative treatments[3]. Locoregional therapies including arterially directed therapies, ablation, and radiotherapy are also associated with good survival outcomes in patients with unresectable disease confined to the liver[4]. However, over 50% of patients with HCC are diagnosed at an advanced stage or with other characteristics that preclude surgical or locoregional treatment[5]. For these patients, systemic therapy is usually the recommended treatment option[4,6].

Over the past 3 years, the number of approved first-line systemic therapies for patients with HCC has expanded greatly, and numerous drugs and drug combinations have been evaluated in this setting[7]. Between 2007 and 2018, sorafenib was the only

approved systemic treatment for HCC based on the results of the Phase III SHARP trial, which showed a survival benefit for sorafenib *vs* placebo[8]. In the decade following the approval of sorafenib, numerous unsuccessful trials of systemic therapies in advanced HCC were conducted until the approval of lenvatinib in 2018[9]. Lenvatinib was approved for first-line use in advanced HCC following the successful outcome of the Phase III REFLECT trial. In this trial, lenvatinib showed a non-inferior overall survival (OS) *vs* sorafenib for the treatment of advanced HCC[10]. Since the approval of lenvatinib, the immunotherapy drugs nivolumab and pembrolizumab, as well as other tyrosine kinase inhibitors (TKI), have been approved for the second-line treatment of HCC. Most recently, combination therapy with the anti-PD-L1 agent atezolizumab plus bevacizumab demonstrated better OS and progression-free survival (PFS) than sorafenib in the Phase III IMbrave 150 trial[11].

The expansion of first-line treatment options for advanced HCC represents a significant advance in the treatment of this disease. However, further data would be useful to inform treatment selection. Most clinical trials of first-line therapies for HCC used placebo or sorafenib as comparators and there are limited data providing a cross comparison of the efficacy and safety of drugs in this setting. Furthermore, although lenvatinib is widely seen as a standard of care in real clinical practice and is a recommended first-line therapy in most international treatment guidelines[4,12,13], there are limited head-to-head data comparing lenvatinib with other systemic therapies. Finally, although historically systemic treatments for HCC were associated with low tumor response rates, recently approved therapies have been associated with response rates > 30%[14]. This has led to renewed interest in tumor response rates in HCC, and investigation of downstaging and conversion therapy strategies. A comparison of response rates for all currently available therapies would therefore be of clinical value.

This network meta-analysis was conducted to systematically review and compare the response rates, survival outcomes, and safety reported by randomized trials of first-line systemic therapies in patients with advanced unresectable HCC, and to provide a comparison between lenvatinib and other systemic therapies in this setting. Two recent meta-analyses have investigated a similar topic to the present study; however, one did not include data on atezolizumab plus bevacizumab and excluded non-targeted therapies[15], and a more recent analysis focused on treatment sequencing by investigating survival outcomes only[16]. Therefore, although there is some overlap with the present analysis, these studies are complementary to each other. In particular, the present analysis is the first to include data on donafenib, a Chinese drug that has shown a superior OS to sorafenib in a Phase III trial[17]. Furthermore, our analysis includes data on survival, response rate, and safety, which in combination are important for treatment decision-making, particularly for patients who may be candidates for downstaging. Finally, the present meta-analysis included a sub-group analysis of patients with HBV infection, which is an important population in the Asia-Pacific region and has not been covered by other current meta-analyses.

MATERIALS AND METHODS

The analysis methods and inclusion criteria for this study were specified in advance and the protocol was prospectively submitted for registration in the PROSPERO database on May 26, 2020. This report has been written in line with the PRISMA guidelines for network meta-analyses.

Eligibility criteria

This analysis included randomized controlled trials conducted in adult patients (age ≥ 18 years) with advanced or unresectable HCC not eligible for, or with disease progression after, surgical or locoregional therapies. Eligible studies included patients with Child-Pugh Class A or B liver function, ≥ 1 measurable lesion, and no evidence of untreated brain or meningeal metastases. Eligible studies were also required to report at least an assessment of tumor response, survival [OS, PFS, or time to progression (TTP)], and safety. The analysis excluded studies including patients with Child-Pugh Class C liver function, patients receiving anticoagulation therapy or antiretroviral therapy for HIV, and patients who had received previous systemic treatment. These broad eligibility criteria covered a number of trials reporting negative results *vs* sorafenib. Although the analysis therefore includes multiple therapies that failed clinical trials in HCC, this allowed the collection of data for sorafenib from studies conducted over a wide time range, which improved the precision of the analysis.

Information sources, search strategy, and study selection

Studies were identified by searching the following electronic databases: PubMed, Science Direct, and the Cochrane Database, and Excerpta Medica Database Abstracts from the American Society of Clinical Oncology (ASCO) 2020 annual congress were also searched. The search was completed on May 21, 2020 using the search terms shown in Figure 1.

The Cochrane risk of bias tool for randomized controlled trials was used to assess the quality and risk of bias of studies included in the analysis[18].

Data extraction

Data were independently extracted by two evaluators (Luo JF and Huang XQ) and cross-checked. In the case of disagreement, the original documents were checked and the correct data confirmed. General information extracted included journal name, document title, publication time, author, country, region where the lead author was located, and the country and region where the research was conducted. Demographics and baseline characteristics extracted were patient age, gender, Barcelona clinic liver cancer classification, Eastern Co-operative Oncology Group performance status, prevalence of HBV infection, and presence of extrahepatic vascular infiltration and extrahepatic metastasis. Details of interventions extracted included dosage and dose schedule. Efficacy and safety endpoints extracted (where available) were overall response rate [ORR; assessed by response evaluation criteria in solid tumours (RECIST) v1/1.1 for all included studies], OS, PFS, TTP, incidence of Grade ≥ 3 adverse events (AE), incidence of treatment interruption due to adverse events (AEs), and incidence of dose reductions due to AEs.

Statistical analysis

For OS, PFS, TTP, and other survival endpoints, hazard ratios (HR) were estimated to compare treatments. For discrete variables such as ORR, and incidence of AEs, estimated risk ratios were calculated to compare treatments. Selection of a fixed effect or random effect model was based on the level of heterogeneity in the data, assessed using the Higgins I^2 statistic and defined as $I^2 \leq 50\%$ and $P > 0.1$. If no obvious data heterogeneity was found, a fixed effect model was adopted, otherwise a random effect model was utilized. For endpoints reported in a relatively small number of studies (< 6), a fixed effects model was adopted.

A network meta-analysis was used to synthesize information from the included studies, and perform direct and indirect comparisons using a method based on the frequency school of Rücker *et al*[19,20]. The Q statistic was used to assess the consistency of direct and indirect evidence in the treatment network(s) studied. If no obvious inconsistency ($P > 0.1$) was found, a fixed effect model was adopted, otherwise a random effect model was utilized. P value, a frequentist analog to the surface under the cumulative ranking curve, was used to rank treatments[21]. A funnel chart was used to evaluate publication bias; a symmetrical graph indicates a low influence of publication bias and an asymmetric graph indicates possible publication bias. A post-hoc analysis of all studies reporting data from patients with HBV-related HCC was also included to assess OS, PFS, and safety in these patients.

All statistical analyses were performed using Rv3.6. The Robias toolkit was used for evaluation of literature quality and Netmeta was used for the network meta-analysis.

RESULTS

Studies included in the analysis

In total, 1398 articles were screened: PubMed/MEDLINE, n = 114; Science Direct, n = 312; Cochrane Database, n = 355; Excerpta Medica Database, n = 561; and the ASCO 2020 abstract book, n = 12 (Figure 1). After removing duplicates and top-line screening of abstracts for suitability, a total of 86 articles were reviewed in detail, of which 27 met the full inclusion criteria (Table 1). These 27 articles corresponded to 27 different studies (Supplementary Figure 1).

Study characteristics

Of the 27 studies included, 25 investigated targeted treatment regimens (nintedanib, mapatumumab + sorafenib, atezolizumab + bevacizumab, doxorubicin + sorafenib, dovitinib, tigatuzumab + sorafenib, vandetanib, brivanib, linifanib, lenvatinib, nivolumab, sunitinib, sorafenib + erlotinib, sorafenib (two studies), nintedanib,

Table 1 Details of included studies

Ref.	Year	Experimental arm(s)	Comparator arm	Primary endpoint	Analysis timing	Survival outcomes, mo
Yen *et al*[47]	2018	Nintedanib	Sorafenib	TTP	PFS: Final; OS: Final	PFS: 2.7 *vs* 3.7; OS: 10.2 *vs* 1.1
Ciuleanu *et al*[48]	2016	Mapatumumab + sorafenib	Placebo + sorafenib	TTP	PFS: Final; OS: Final	PFS: 3.2 *vs* 4.3; OS: 10.0 *vs* 10.1
Finn *et al*[11]	2020	Atezolizumab + bevacizumab	Sorafenib	OS and PFS	PFS: Final; OS: Final	PFS: 6.8 *vs* 4.3; OS: NE *vs* 13.2
Abou-Alfa *et al*[49]	2010	Doxorubicin + sorafenib	Doxorubicin + placebo	TTP	PFS: Final; OS: Final	PFS: 6.0 *vs* 2.7; OS: 13.7 *vs* 6.5
Cheng *et al*[50]	2016	Dovitinib	Sorafenib	OS and TTP	TTP: Final; OS: Final	TTP: 4.1 *vs* 4.1; OS: 8.0 *vs* 8.4
Cheng *et al*[28]	2015	Tigatuzumab (6 + 2) + sorafenib; Tigatuzumab (6 + 6) + sorafenib	Sorafenib	TTP	TTP: Final; OS: Final	TTP: 3.0 *vs* 3.9 *vs* 2.8; OS: 8.2 *vs* 12.2 *vs* 8.2
Hsu *et al*[51]	2012	Vandetanib 300 mg/d; Vandetanib 100 mg/d	Placebo	Tumor stabilization rate	PFS: Final; OS: Final	PFS: 1.1 *vs* 0.7 *vs* 1.0; OS: 6.0 *vs* 5.8 *vs* 4.3
Johnson *et al*[22]	2013	Sorafenib	Brivanib	OS	PFS: No; OS: Final	PFS: 4.1 *vs* 4.2; OS: 9.9 *vs* 9.5
Cainap *et al*[24]	2015	Linifanib	Sorafenib	OS	PFS: Final; OS: Final	PFS: 4.2 *vs* 2.9; OS: 9.1 *vs* 9.8
Kudo *et al*[10]	2018	Lenvatinib	Sorafenib	OS	PFS: No; OS: Final	PFS: 7.4 *vs* 3.7; OS: 13.6 *vs* 12.3
Yau *et al*[23]	2019	Nivolumab	Sorafenib	OS	PFS: Final; OS: Final	PFS: 3.7 *vs* 3.8; OS: 16.4 *vs* 14.7
Cheng *et al*[29]	2013	Sunitinib	Sorafenib	OS	PFS: Final;OS: Final	PFS: 3.6 *vs* 3.0; OS: 7.9 *vs* 10.2
Zhu *et al*[26]	2015	Sorafenib + erlotinib	Sorafenib + placebo	OS	TTP: Final; OS: Final	TTP: 3.2 *vs* 4.0; OS: 9.5 *vs* 8.5
Llovet *et al*[52]	2008	Sorafenib	Placebo	OS and TTP	TTP: Final; OS: Final	TSP: 5.5 *vs* 2.8; OS: 10.7 *vs* 7.9
Cheng *et al*[25]	2009	Sorafenib	Placebo	-	TTP: Final; OS: Final	TTP: 2.8 *vs* 1.4; OS: 6.5 *vs* 4.2
Palmer *et al*[53]	2018	Nintedanib	Sorafenib	TTP	PFS: Final; OS: Final	PFS: 5.3 *vs* 3.9; OS: 11.9 *vs* 11.4
Thomas *et al*[54]	2018	Bevacizumab + erlotinib	Sorafenib	OS	PFS: No; OS: Final	PFS: 4.4 *vs* 2.8; OS: 8.6 *vs* 8.6
Abou-Alfa *et al*[55]	2019	Sorafenib + doxorubicin	Sorafenib	OS	PFS: Final; OS: Final	PFS: 4.0 *vs* 3.7; OS: 9.3 vs. 9.4
Tak *et al*[27]	2018	Sorafenib	Sorafenib + resminostat	TTP	TTP: Final; OS: Final	TTP: 2.8 *vs* 2.8; OS: 14.1 *vs* 11.8
Jouve *et al*[56]	2019	Sorafenib + pravastatin	Sorafenib	OS	PFS: Final; OS: Final	PFS: 5.0 *vs* 5.4; OS: 10.7 *vs* 10.5
Lee *et al*[57]	2016	AEG35156 + sorafenib	Sorafenib	PFS	PFS: Final; OS: Final	PFS: 4.0 *vs* 2.6; OS: 6.5 *vs* 5.4
Assenat *et al*[58]	2019	Sorafenib + GEMOX	Sorafenib	PFS	PFS: Final; OS: Final	PFS: 6.2 *vs* 4.6; OS:13.5 *vs* 14.8
Azim *et al*[59]	2018	Sorafenib + tegafur–uracil	Sorafenib	TTP	PFS: Final; OS: Final	PFS: 6.0 *vs* 6.0; OS: 8.2 *vs* 10.5
Koeberle *et al*[60]	2016	Sorafenib	Sorafenib + everolimus	PFS	PFS: Final; OS: Final	PFS: 6.6 *vs* 5.7; OS: 10.0 *vs* 12
Bi *et al*[17]	2020	Donafinib	Sorafenib	OS	PFS: Final; OS: Final	PFS: 3.7 *vs* 3.6; OS: 21.1 *vs* 10.3
Qin *et al*[61]	2013	FOLFOX4	Doxorubicin	OS	PFS: Final; OS: Final	PFS: 2.9 *vs* 1.8; OS: 6.4 *vs* 5.0

Yeo *et al*[62]	2005	Doxorubicin	PIAF	OS	PFS: No; OS: Final	OS: 6.8 *vs* 8.7

FOLFOX4: Oxaliplatin/folinic acid/5-fluorouracil; GEMOX: Gemcitabine and oxaliplatin; NE, Not reported; OS, Overall survival; PFS, Progression-free survival; PIAF, Cisplatin/interferon α-2b/doxorubicin/5-fluorouracil; TTP, Time to progression.

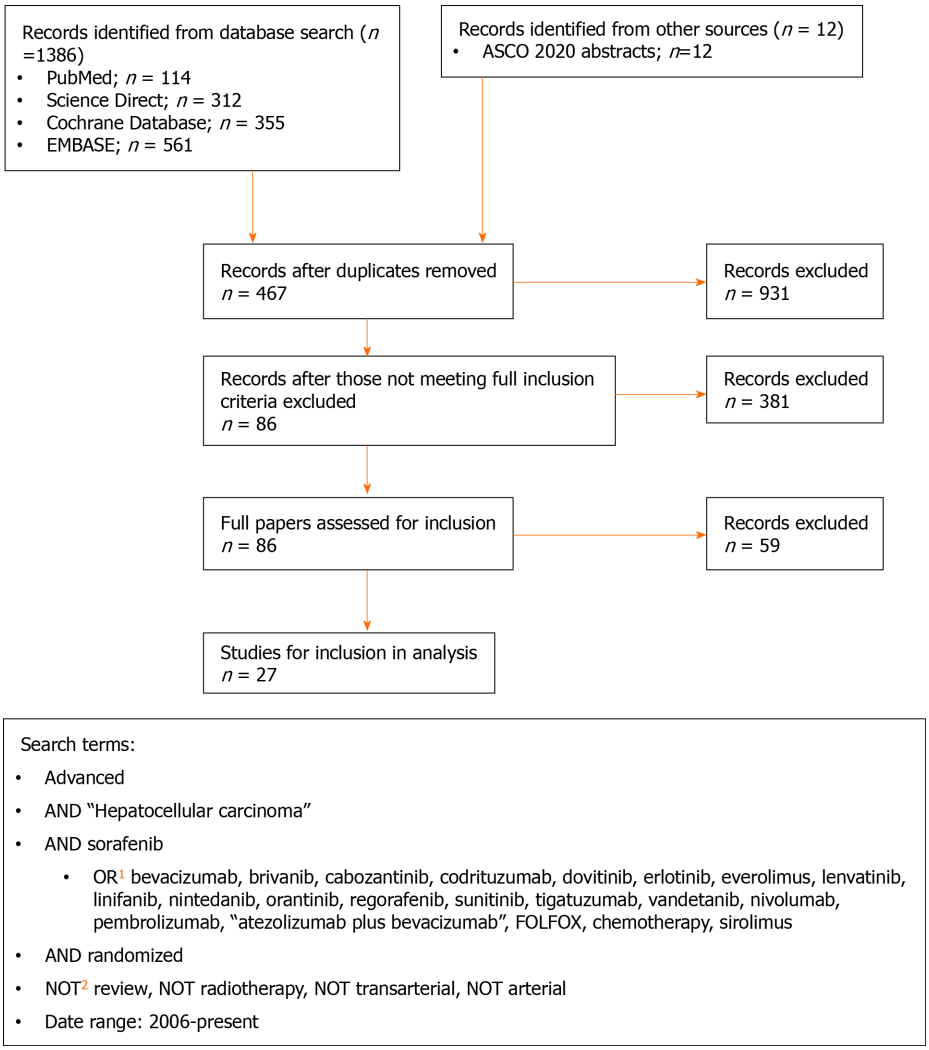


Figure 1 Flow chart of study selection and search terms. Different therapeutics were searched for using individual searches to allow easier processing of the results; NOT was used for databases allowing use of this operator. ASCO: American Society of Clinical Oncology.

bevacizumab + erlotinib, sorafenib + doxorubicin, sorafenib + resminostat, sorafenib + pravastatin, AEG35156 (a second-generation synthetic antisense oligonucleotide inhibitor of cellular expression of the X-linked inhibitor of apoptosis protein) + sorafenib, sorafenib + gemcitabine and cisplatin, sorafenib + tegafur–uracil, sorafenib + everolimus, and donafinib) and two investigated combination chemotherapy regimens [oxaliplatin/folinic acid/5-fluorouracil (FOLFOX4) and cisplatin/interferon α-2b/doxorubicin/5-fluorouracil] (Table 1). Twenty-one of the included studies used sorafenib as the comparator treatment, three used doxorubicin, and three studies were placebo controlled (including the two Phase III studies of sorafenib). The majority of the studies had OS (n = 12) or PFS/TTP (n = 10) as the primary endpoint, and almost all had reported final data for these endpoints.

Quality assessment

Study design characteristics are summarized in Supplementary Table 1. In brief, all 27 studies selected for inclusion were randomized controlled studies (20 provided details of the randomization scheme used and seven articles did not specify), seven of the studies used double blinding and 20 were open label, and 24 included a data flow

chart. Overall, the quality of the included studies was considered relatively high (Figure 1).

Patient description

All of the studies included patients with advanced HCC who had not received previous treatment. Overall, the total of 10256 patients included in the analysis were predominantly male and had median ages ranging from 49 to 68 years, and most of the studies included > 50% of patients with extrahepatic metastasis (Table 2).

Evaluation of efficacy

Overall response rate: A total of 18 studies reported ORR, including 19 interventions and allowing 20 comparisons (Figure 2A). No significant heterogeneity was detected between the studies (tau-squared = 0; I^2 = 0%; P = 0.9502) and a fixed effect model was selected. P value for ORR showed that lenvatinib was associated with the best ORR among all treatments included in the analysis (P = 0.9042) (Figure 2B). Atezolizumab + bevacizumab ranked second (P = 0.8045) and nivolumab ranked third (P = 0.7834). Using lenvatinib as the comparator, all treatments included in the analysis had an estimated risk ratio for ORR (RR_{ORR}) of < 1, except for AEG35156 + sorafenib, which had an estimated RR_{ORR} of 1.3451 [95% confidence interval (CI): 0.07-25.21] (Figure 2B).

Progression-free survival: A total of 15 studies reported PFS, including 15 interventions and allowing 15 comparisons (Figure 3A). No significant heterogeneity was detected (tau-squared = 0; I^2 = 0%; P = 0.7361) and a fixed effect model was selected. Atezolizumab + bevacizumab was ranked first for PFS (P = 0.9501), followed by lenvatinib (P = 0.9041). Nivolumab ranked sixth (P = 0.558) (Figure 3B). With the exception of atezolizumab + bevacizumab (HR_{PFS} = 0.90; 95%CI: 0.64-1.25), the estimated HRs for PFS for all included treatments *vs* lenvatinib were > 1; however, the associated 95%CI passed through unity for bevacizumab plus erlotinib, linifanib, and FOLFOX4.

Time to progression: A total of 17 studies reported TTP, including 17 interventions and allowing 19 comparisons (Figure 3C). No significant heterogeneity was detected between studies (tau-squared = 0; I^2 = 0%; P = 0.9028) and a fixed effect model was selected. Lenvatinib was ranked first for TTP (P = 0.9888) followed by linifanib (P = 0.9067) and sorafenib + doxorubicin (P = 0.7344) (Figure 3D). When compared with lenvatinib, all other treatments in the analysis had an estimated HR_{TTP} > 1, although the associated 95%CI passed through unity for linifanib and sorafenib plus tegafur–uracil.

Overall survival: A total of 24 studies reported OS, including 25 interventions and allowing 28 comparisons (Figure 3E). No significant heterogeneity was detected between studies (tau-squared = 0; I^2 = 0%; P = 0.9802) and a fixed effect model was selected. Atezolizumab + bevacizumab was ranked highest for OS (P = 0.9651) followed by vandetanib 100 mg/d (P = 0.8653), donafinib (P = 0.7958), and nivolumab (P = 0.7701) (Figure 3F). Lenvatinib ranked sixth (P = 0.6675). Atezolizumab + bevacizumab was associated with a lower risk of death *vs* lenvatinib (HR_{os} = 0.63; 95%CI: 0.44-0.89), and the HR_{os} for most other treatments *vs* lenvatinib had associated 95%CIs that passed through unity.

Outcomes in patients with HBV infection: Ten studies included sub-analyses of patients with HBV infection, including data on the following treatments: atezolizumab + bevacizumab[11], brivanib[22], nivolumab[23], lenvatinib[10], linifanib[24], sorafenib[25], sorafenib + erlotinib[26], sorafenib + resminostat[27], tigatuzumab + sorafenib[28], and sunitinib[29]. A total of three studies reported PFS in patients with HBV infection, including four interventions and three comparisons (Supplementary Figure 2A). A fixed effect model was selected for the analysis. Lenvatinib ranked first for PFS (P = 0.8786) followed by atezolizumab + bevacizumab (P = 0.7746) and donafinib (P = 0.2972) (Figure 2B). A comparison of HRs for PFS *vs* lenvatinib is shown in Supplementary Figure 2B. A total of nine studies reported OS, including ten interventions and allowing nine comparisons (Supplementary Figure 2C). A random effect model was selected for the analysis. Atezolizumab + bevacizumab ranked first (P = 0.9751), followed by lenvatinib (P = 0.8308) and nivolumab (P = 0.7732) (Supplementary Figure 2D). Comparison with lenvatinib revealed that atezolizumab + bevacizumab had an estimated HR_{OS} < 1 and all other interventions had an HR_{OS} > 1 (Supplementary Figure 2D).

Table 2 Patient characteristics in the included studies

Ref.	Year	Treatments	*n*	Age, median	Males, %	ECOG 0/1–2, %	Extrahepatic disease, %
Yen *et al*[47]	2018	Nintedanib	63	58	91	55.6/44.5	68.3
		Sorafenib	32	62	81	56.3/43.8	68.3
Ciuleanu *et al*[48]	2016	Mapatumumab + sorafenib	50	60	52	36.0/64.0	66.0
		Placebo + sorafenib	51	61	77	33.3/66.6	49.0
Finn *et al*[11]	2020	Atezolizumab + bevacizumab	336	64	82	62.0/38.0	63.0
		Sorafenib	165	66	83	62.0/38.0	56.0
Abou-Alfa *et al*[49]	2010	Doxorubicin + sorafenib	47	66	66	-	51.1
		Doxorubicin + placebo	49	65	86	-	79.6
Cheng *et al*[50]	2016	Dovitinib	82	56	89	63.0/37.0	-
		Sorafenib	83	56	81	64.0/35.0	-
Cheng *et al*[28]	2015	Tigatuzumab (6 + 2) + sorafenib	53	63	85	60.4/39.6	-
		Tigatuzumab (6 + 6) + sorafenib	54	63	83	57.4/42.6	-
		Sorafenib	55	66	80	54.5/45.5	-
Hsu *et al*[51]	2012	Vandetanib 300 mg/d	19	55	95	-	-
		Vandetanib 100 mg/d	25	61	68	-	-
		Placebo	23	56	87	-	-
Johnson *et al*[22]	2013	Sorafenib	578	60	84	61.0/39.0	62.0
		Brivanib	577	61	84	64.0/36.0	63.0
Cainap *et al*[24]	2015	Linifanib	514	59	86	62.8/37.2	59.7
		Sorafenib	521	60	84	66.2/33.8	56.8
Kudo *et al*[10]	2018	Lenvatinib	478	63	85	-	-
		Sorafenib	476	62	84	-	-
Yau *et al*[23]	2019	Nivolumab	371	65	85	-	-
		Sorafenib	372	65	85	-	-
Cheng *et al*[29]	2013	Sunitinib	530	59	82	52.5/46.8	78.9
		Sorafenib	544	59	84	52.9/46.7	76.3
Zhu *et al*[26]	2015	Sorafenib + erlotinib	362	60	82	61.3/38.7	56.6
		Sorafenib + placebo	358	61	80	60.3/39.7	61.2
Llovet *et al*[52]	2008	Sorafenib	299	65	87	54.0/46.0	53.0
		Placebo	303	66	87	54.0/46.0	50.0
Cheng *et al*[25]	2009	Sorafenib	150	51	85	25.3/74.6	68.7
		Placebo	76	52	87	27.6/72.4	68.4
Palmer *et al*[53]	2018	Nintedanib	62	66	77	51.6/48.4	64.5
		Sorafenib	31	64	84	58.1/33.0	67.7
Thomas *et al*[54]	2018	Bevacizumab + erlotinib	47	61	NR	32.0/68.0	40.0
		Sorafenib	43	61	NR	40.0/60.0	25.0
Abou-Alfa *et al*[55]	2019	Sorafenib + doxorubicin	180	62	85	36.1/63.9	-
		Sorafenib	176	62	87	39.8/60.2	-

Tak *et al*[27]	2018	Sorafenib	84	62	87	-	56.0
		Sorafenib + resminostat	86	65	80	-	51.8
Jouve *et al*[56]	2019	Sorafenib + pravastatin	162	68	96	-	29.0
		Sorafenib	161	68	88	-	30.4
Lee *et al*[57]	2016	AEG35156 + sorafenib	31	61	87	3.2/96.8	-
		Sorafenib	17	54	88	11.8/88.3	-
Assenat *et al*[58]	2019	Sorafenib + GEMOX	39	62	86	-	77.0
		Sorafenib	44	65	92	-	61.0
Azim *et al*[59]	2018	Sorafenib + tegafur–uracil	36	59	86	69.4/30.6	52.8
		Sorafenib	38	59	90	65.8/34.2	47.4
Koeberle *et al*[60]	2016	Sorafenib	46	65	87	72.0/28.0	57.0
		Sorafenib + everolimus	59	66	81	59.0/41.0	54.0
Bi *et al*[17]	2020	Donafinib	328	53	86	61.3/38.7	-
		Sorafenib	331	53	88	66.8/33.2	-
Qin *et al*[61]	2013	FOLFOX4	184	50	90	-	-
		Doxorubicin	187	49	87	-	-
Yeo *et al*[62]	2005	Doxorubicin	94	54	90	87.2/12.8	-
		PIAF	94	49	93	92.6/7.4	-

ECOG: Eastern Co-operative Oncology Group; FOLFOX4: Oxaliplatin/folinic acid/5-fluorouracil; GEMOX: Gemcitabine and oxaliplatin; NR: Not reported; PIAF: Cisplatin/interferon α-2b/doxorubicin/5-fluorouracil.

Safety

Grade ≥ 3 adverse events: In total, 17 studies reported data on the incidence of Grade ≥ 3 AEs, including 19 interventions and allowing 21 comparisons (Supplementary Figure 3A). No significant heterogeneity was detected between studies (tau-squared = 0; I^2 = 0%; P = 0.4493) and a fixed effect model was selected. Nivolumab ranked 2/19 (P = 0.9351), sorafenib ranked 8/19 (P = 0.5040), atezolizumab + bevacizumab ranked 11/19 (P = 0.4167), and lenvatinib ranked 16/19 (P = 0.2468) for incidence of Grade ≥ 3 AEs (higher ranking indicated a lower incidence of AEs) (Supplementary Figure 3B).

Treatment termination due to adverse events: A total of 13 studies reported the incidence of treatment termination due to AEs, including 13 interventions and allowing 15 comparisons (Supplementary Figure 3C). A degree of heterogeneity was detected between studies (tau-squared = 0.1536; I^2 = 65%; P = 0.0573) and a random effect model was selected. After ranking all interventions from the lowest to highest incidence of terminations due to AEs, vandetanib 300 mg/d and 100 mg/d were ranked first and second (P = 0.8036 and 0.7252, respectively), sorafenib ranked 5/13 (P = 0.5372), nintedanib ranked 8/13 (P = 0.4251), lenvatinib ranked 10/13 (P = 0.3907), and atezolizumab + bevacizumab ranked 13/13 (P = 0.2584) (Supplementary Figure 3D).

DISCUSSION

Following an expansion of first-line systemic treatment options for HCC over the past decade, international treatment guidelines now recommend sorafenib, lenvatinib, and atezolizumab plus bevacizumab in this setting, as well as nivolumab and FOLFOX (off-label use in many countries, but approved by the China National Medical Products Administration) for selected patients[4,12,13]. Numerous other therapies and combinations of therapies have also been unsuccessfully investigated in first-line advanced HCC management. However, most trials of systemic therapy for HCC used sorafenib as the comparator, as it was the only approved systemic therapy available at the time, and this limits the clinicians' ability to compare currently available treatment options. The present study represents one of the most comprehensive systematic

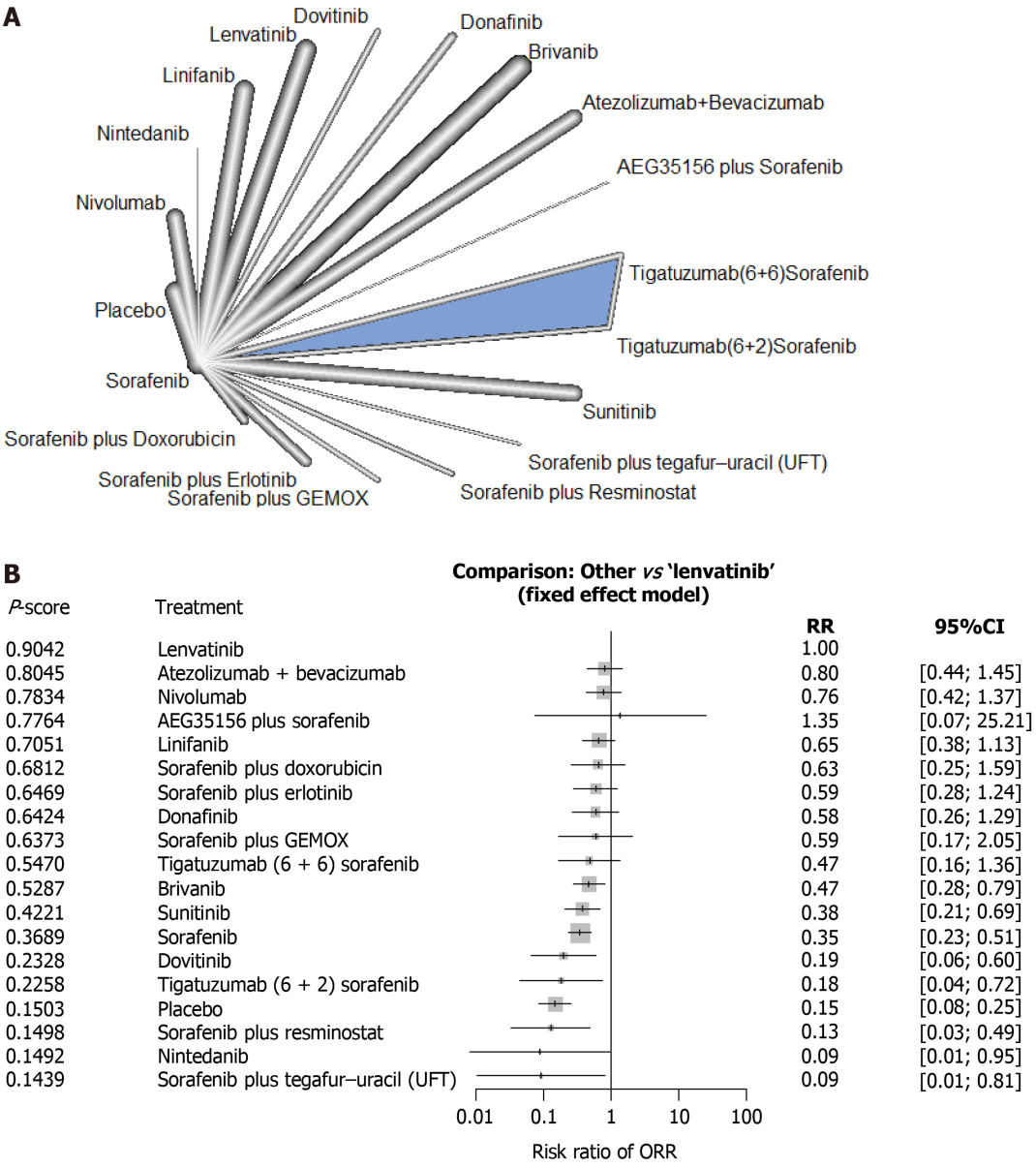
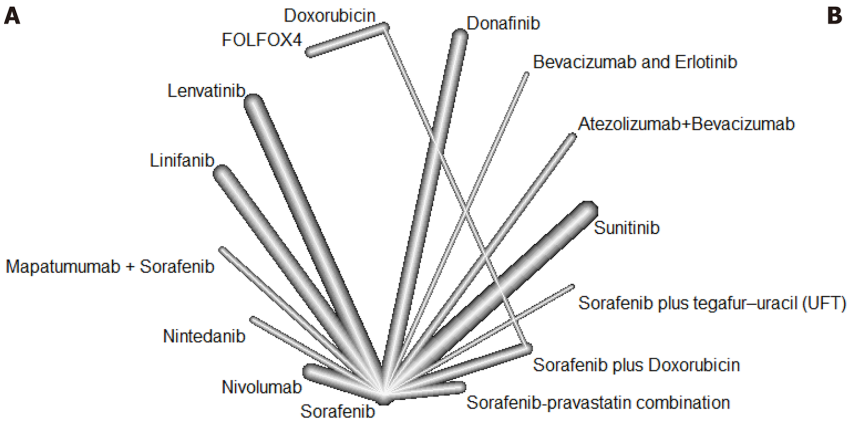


Figure 2 Response rates of first-line systemic therapy in patients with advanced hepatocellular carcinoma. A: Network diagram; B: Interventions ranked by *P* value with risk ratios and 95% confidence interval for overall response rate for each treatment *vs* lenvatinib. CI: Confidence interval; GEMOX: Gemcitabine and oxaliplatin; ORR: Overall response rate; RR: Risk ratio.

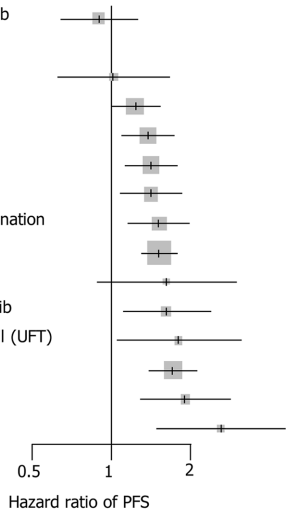
reviews and meta-analyses of first-line systemic treatments for advanced unresectable HCC conducted to date, and compares the treatment outcomes and safety of lenvatinib with multiple other systemic therapies, including immunotherapy (nivolumab) and combined therapy with immunotherapy and a TKI (atezolizumab + bevacizumab).

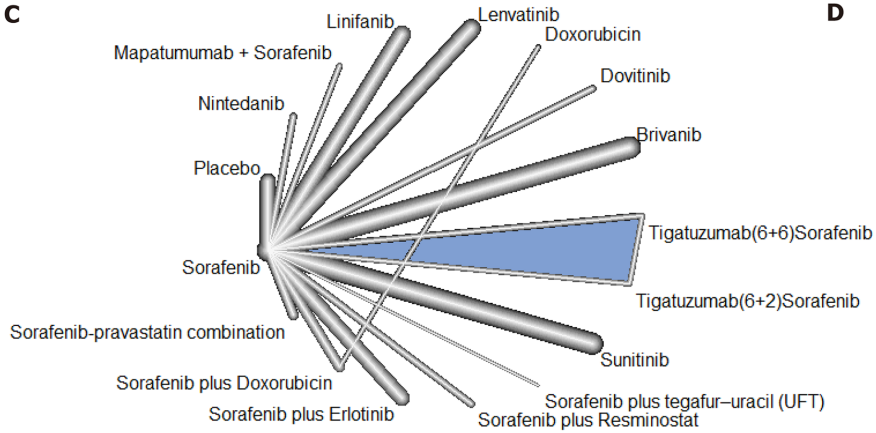
Our results show that atezolizumab plus bevacizumab is associated with the best OS outcomes of all therapies included in the analysis. This result is supported by findings from a recent meta-analysis that investigated optimal treatment sequencing for HCC and also reported that atezolizumab plus bevacizumab had a higher OS benefit *vs* lenvatinib (HR_{OS} = 0.63; 95%CI: 0.44-0.89), nivolumab (HR_{OS} = 0.68; 95%CI: 0.48-0.98), and sorafenib (HR_{OS} = 0.58; 95%CI: 0.42-0.80)[16]. Atezolizumab plus bevacizumab is the first combined immunotherapy and vascular-targeted regimen to be recommended as a first-line treatment option in the National Comprehensive Cancer Network HCC guidelines[4]. The long OS associated with atezolizumab plus bevacizumab may be related to the 'long tail' effect characteristic of immune checkpoint inhibitors, which was also observed in the Phase III Checkmate 459 study of nivolumab. A number of studies have identified several mechanisms by which angiogenesis-related processes can enhance immune checkpoint inhibitors therapy, including vascular normalization, reduction of hypoxia, and increasing tumor infilt-



B

P-score	Treatment	HR [95%CI]
0.9501	Atezolizumab + bevacizumab	0.89 [0.64; 1.25]
0.9041	Lenvatinib	1.00
0.8490	Bevacizumab and erlotinib	1.02 [0.62; 1.66]
0.7411	Linifanib	1.23 [0.99; 1.53]
0.5899	Donafinib	1.38 [1.09; 1.73]
0.5548	Nivolumab	1.41 [1.13; 1.76]
0.5511	Sorafenib plus doxorubicin	1.41 [1.08; 1.84]
0.4347	Sorafenib-pravastatin combination	1.52 [1.16; 1.98]
0.4246	Sorafenib	1.52 [1.30; 1.76]
0.3951	FOLFOX4	1.62 [0.88; 2.97]
0.3599	Mapatumumab plus sorafenib	1.63 [1.10; 2.37]
0.2738	Sorafenib plus tegafur–uracil (UFT)	1.80 [1.05; 3.10]
0.2422	Sunitinib	1.71 [1.40; 2.10]
0.1883	Nintedanib	1.91 [1.29; 2.83]
0.0414	Doxorubicin	2.61 [1.49; 4.56]

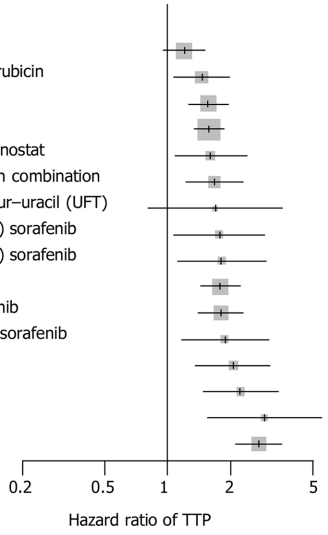




D

Comparison: Other *vs* 'lenvatinib' (fixed effect model)

P-score	Treatment	HR [95%CI]
0.9888	Lenvatinib	1.00
0.9067	Linifanib	1.20 [0.96; 1.52]
0.7344	Sorafenib plus doxorubicin	1.46 [1.08; 1.97]
0.6562	Brivanib	1.57 [1.27; 1.94]
0.6484	Sorafenib	1.59 [1.35; 1.86]
0.5944	Sorafenib plus resminostat	1.61 [1.08; 2.40]
0.5426	Sorafenib-pravastatin combination	1.68 [1.23; 2.31]
0.5265	Sorafenib plus tegafur–uracil (UFT)	1.70 [0.81; 3.57]
0.4797	Tigatuzumab (6 + 2) sorafenib	1.78 [1.07; 2.95]
0.4473	Tigatuzumab (6 + 6) sorafenib	1.83 [1.13; 2.95]
0.4370	Sunitinib	1.79 [1.45; 2.23]
0.4360	Sorafenib plus erlotinib	1.80 [1.41; 2.30]
0.4081	Mapatumumab plus sorafenib	1.89 [1.17; 3.05]
0.3013	Nintedanib	2.07 [1.37; 3.13]
0.2222	Dovitinib	2.25 [1.50; 3.39]
0.1003	Doxorubicin	2.92 [1.56; 5.46]
0.0702	Placebo	2.76 [2.14; 3.55]



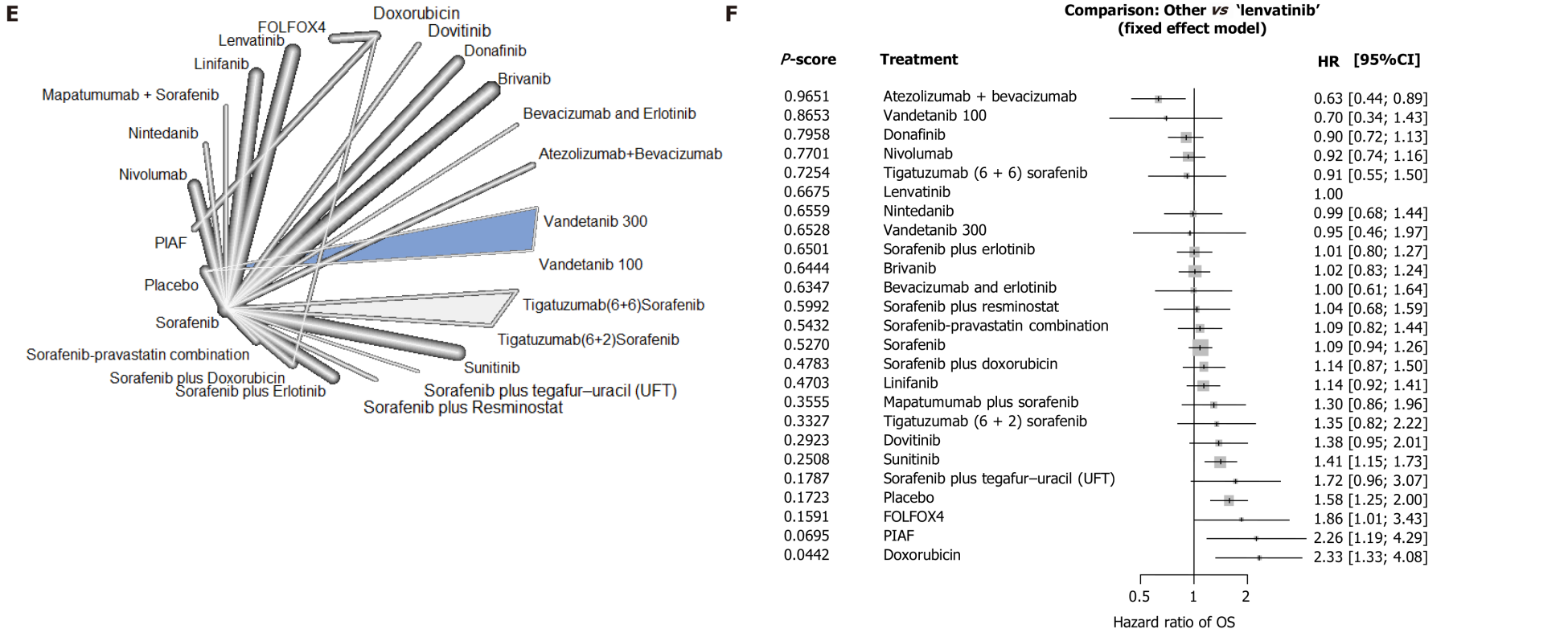


Figure 3 Survival outcomes in patients with advanced hepatocellular carcinoma following first-line systemic therapy. A, C, and E: Network diagrams; B: Interventions ranked by *P* value with hazard ratios for progression-free survival, D: Time to progression and F: overall survival for each treatment *vs* lenvatinib. CI: Confidence interval; FOLFOX4: Oxaliplatin/folinic acid/5-fluorouracil; HCC: Hepatocellular carcinoma; HR: Hazard ratio; OS: Overall survival; PIAF: Cisplatin/interferon α-2b/doxorubicin/5-fluorouracil; TTP: Time to progression.

rating lymphocytes[30]. Although bevacizumab monotherapy failed Phase II trials in unresectable HCC, in combination with atezolizumab it led to superior efficacy compared with bevacizumb monotherapy[31]. However, consideration of treatment safety and tolerability is also an important factor in clinical decision-making. Our analysis revealed that atezolizumab plus bevacizumab was associated with the highest incidence of discontinuation due to AEs. This may be associated with the relatively long time to progression and duration of treatment reported for atezolizumab plus bevacizumab, but as treatment discontinuations due to AEs usually involve uncontrolled Grade ≥ 3 AEs, this would likely be a weak association. In addition, the prescribing information for bevacizumab highlights a possible risk of bleeding, and requires termination of bevacizumab at least 4 wk before surgery[32]. Therefore, in

patients with high risk of gastric esophageal varices and patients with the potential to undergo any surgical procedures, atezolizumab plus bevacizumab should be used carefully, to manage the risk of bleeding events. Atezolizumab plus bevacizumab may be more suitable for patients who are unsuitable for surgery but with good liver function and limited cirrhosis, who have the potential to achieve a long-term survival benefit with systemic therapy.

The results of this meta-analysis show that there is currently not one single systemic treatment for advanced HCC associated with superior outcomes across all outcome measurements (ORR, OS, PFS, and safety). This highlights the importance of individualized treatment selection based on specific treatment goals. For example, a number of studies have shown that lenvatinib or lenvatinib combination therapy[33] can allow patients to achieve downstaging and become eligible for surgery[34-36]. For patients with HCC ineligible for surgical intervention at diagnosis, we are of the opinion that treatment selection should be objective based. In patients without serious underlying liver disease and for whom surgery may be possible, systemic treatments with the highest ORR are the optimal choice. Conversely, for patients with poor liver function, underlying liver disease, or local advanced HCC, selection of therapies based on longer OS may provide the most benefit.

In our analysis, lenvatinib had superior short-term efficacy compared with all other systemic therapies investigated. Lenvatinib ranked first for ORR and TTP, and second for PFS after atezolizumab plus bevacizumab. This finding is supported by the results of another recent network meta-analysis presented at the ASCO Gastrointestinal Symposium 2021 that also ranked atezolizumab plus bevacizumab first for OS but lenvatinib first for ORR[37]. In addition, although direct comparison of the ORRs (RECIST v1.1) reported for atezolizumab plus bevacizumab and lenvatinib in the IMbrave 100 and REFLECT studies appears to show a moderately higher ORR for atezolizumab plus bevacizumab (27% *vs* 18%)[10,11], our network analysis provides a more robust comparison of the two therapies by comparing both to sorafenib. There are several possible mechanistic explanations for this finding. First, preclinical studies show that lenvatinib has multiple targets including VEGFR1-3, FGFR1-4, PDGFRα, RET, and KIT, and this broad spectrum of activity may be one factor explaining the high response rates associated with this therapy[38]. Furthermore, lenvatinib is a type V TKI with fast binding and relatively slow dissociation compared with other TKIs[39]. In addition to anti-vascular effects, lenvatinib also has a regulatory effect on the immune microenvironment of liver cancer[40]. Preclinical research has shown that, compared with sorafenib, lenvatinib has a significant anti-tumor effect in immunodeficient mice, suggesting that lenvatinib may activate immune function by decreasing the number of tumor-associated macrophages, increasing the proportion of activated CD8+ cells[40], and increasing activation and infiltration of natural killer cells[41].

HBV-related liver cancer is particularly prevalent in Asian populations, especially in China where 69%-80% of liver cancers have an HBV etiology[42,43]. Our meta-analysis of data from patients with HCC and HBV infection suggested that, in terms of OS, atezolizumab plus bevacizumab, lenvatinib, and nivolumab are the three most effective treatments in this patient population. For PFS, lenvatinib ranked first over atezolizumab plus bevacizumab. This finding supports previous meta-analyses that have shown lenvatinib to have a particularly strong anti-tumor effect *vs* sorafenib in patients with HBV-related HCC[44,45]. It is unclear why lenvatinib may have a particularly good anti-tumor effect in HBV-related HCC, but it may be due to the impact of lenvatinib on the immune microenvironment, as described above. In addition, the China National Health and Health Commission guidelines for diagnosis and treatment of primary liver cancer in China (2019 edition) recommend lenvatinib as a systemic therapy with good efficacy in patients with HBV-related liver cancer[46].

This network meta-analysis had several possible limitations. First, the quality of studies included in the analysis had some heterogeneity; for example, the analysis included both large Phase III clinical trials, such as REFLECT and Checkmate 459, and smaller Phase II clinical studies. Second, there was also heterogeneity in the patient populations included in the analysis, including patients from different geographic regions, of different races, and different proportions of patients with HBV infection. Additionally, it should be noted that second-line therapeutic options for HCC have greatly improved over the past decade. As a result, estimates of first-line OS from older studies are generally shorter than those from more recent studies. However, among the therapies included in this analysis that are currently approved for first-line HCC, only sorafenib has OS data old enough to potentially be biased by this phenomenon. Fortunately, our analysis was based on pooled data from the pivotal study of sorafenib in 2008 and comparator arms of trials conducted between 2008 and 2020, which limits the potential effect of bias from improvements in second-line

therapies[47-62]. Finally, because multiple interventions were included in the analysis, several had data from only one study and therefore a relatively small sample size, which may have led to bias.

CONCLUSION

This network meta-analysis of first-line systemic therapies for advanced HCC revealed that atezolizumab plus bevacizumab is associated with the best OS and PFS, but also with a high incidence of discontinuation due to AEs. The results also showed that lenvatinib is associated with the best ORR of all systemic therapies included in the analysis, as well as a relatively high PFS, particularly in patients with HBV-related liver cancer in whom lenvatinib ranked first for PFS, over atezolizumab plus bevacizumab. Therefore, in patients with unresectable advanced HCC, systemic treatment should be selected based on the individualized treatment goals of each patient.

ARTICLE HIGHLIGHTS

Research background

The recent expansion of first-line systemic therapy options for patients with advanced hepatocellular carcinoma represents a significant advance in the treatment of this disease. However, the majority of clinical trials in first-line hepatocellular carcinoma management used placebo or sorafenib as comparators, and there are limited data providing a cross comparison of the efficacy and safety of treatments in this setting, especially for newly-approved immune checkpoint inhibitor and vascular endothelial growth factor inhibitor combination treatments.

Research motivation

Clinical trials of recently-approved therapies for hepatocellular carcinoma have revealed differing profiles of efficacy and safety, and comparative data to inform selection of first-line treatments for individual patients are limited. Furthermore, although lenvatinib is widely seen as a standard of care in real clinical practice, and is a recommended first-line therapy in most international treatment guidelines, there are limited head-to-head data comparing lenvatinib with other systemic therapies.

Research objectives

The objectives of this network meta-analysis were to systematically review and compare the response rates, survival outcomes, and safety of first-line systemic therapies for advanced hepatocellular carcinoma, and to provide a comparison between lenvatinib and other systemic therapies in this setting. The study also included a sub-group analysis of patients with hepatitis B virus infection, which is an important population in the Asia-Pacific region and has not been covered by other current meta-analyses.

Research methods

We searched PubMed, Science Direct, the Cochrane Database, Excerpta Medica Database, and abstracts from the American Society of Clinical Oncology 2020 annual congress. Eligible studies were randomized controlled trials of systemic therapy enrolling adults with advanced/unresectable hepatocellular carcinoma. A network meta-analysis was used to synthesize data and perform direct and indirect comparisons between treatments for endpoints including (where available) overall response rate, overall survival, progression-free survival, time-to-progression, incidence of Grade ≥ 3 adverse events, incidence of treatment interruptions due to adverse events, and incidence of dose reductions due to adverse events. *P* value, a frequentist analog to the surface under the cumulative ranking curve, was used to rank treatments.

Research results

Treatments included in the analysis were atezolizumab plus bevacizumab, brivanib, donafenib, dovitinib, FOLFOX4, lenvatinib, linifanib, nintedanib, nivolumab, sorafenib, sunitinib, vandetanib, 11 sorafenib combination therapies, and three other

combination therapies. Atezolizumab plus bevacizumab was ranked first for progression-free survival and overall survival but also had the highest rate of discontinuations due to adverse events. Lenvatinib ranked first for overall response rate and second for progression-free survival. Our findings show that first-line systemic treatment should be selected based on individualized treatment goals and provide valuable comparative data that can help to inform treatment decisions.

Research conclusions

Our findings suggest that there is no one single first-line treatment for advanced hepatocellular carcinoma associated with superior outcomes across all outcome measurements. Therefore, first-line systemic treatment should be selected based on individualized treatment goals.

Research perspectives

Future research should continue to evaluate new therapeutic strategies for hepatocellular carcinoma in the context of existing treatments, and provide further information to support treatment selection for individual patients.

REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Zhou M**, Wang H, Zhu J, Chen W, Wang L, Liu S, Li Y, Liu Y, Yin P, Liu J, Yu S, Tan F, Barber RM, Coates MM, Dicker D, Fraser M, González-Medina D, Hamavid H, Hao Y, Hu G, Jiang G, Kan H, Lopez AD, Phillips MR, She J, Vos T, Wan X, Xu G, Yan LL, Yu C, Zhao Y, Zheng Y, Zou X, Naghavi M, Wang Y, Murray CJ, Yang G, Liang X. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. *Lancet* 2016; **387**: 251-272 [PMID: 26510778 DOI: 10.1016/S0140-6736(15)00551-6]

3 **Allemann P**, Demartines N, Bouzourene H, Tempia A, Halkic N. Long-term outcome after liver resection for hepatocellular carcinoma larger than 10 cm. *World J Surg* 2013; **37**: 452-458 [PMID: 23188527 DOI: 10.1007/s00268-012-1840-5]

4 **National Comprehensive Cancer Network**. Hepatobiliary cancers 2020 [cited 20 March 2021]. Available from: https://www.abc-directory.com/site/1034756

5 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/Liv.12818]

6 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

7 **Li D**, Sedano S, Allen R, Gong J, Cho M, Sharma S. Current Treatment Landscape for Advanced Hepatocellular Carcinoma: Patient Outcomes and the Impact on Quality of Life. *Cancers (Basel)* 2019; **11** [PMID: 31216701 DOI: 10.3390/cancers11060841]

8 **Bruix J**, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; **57**: 821-829 [PMID: 22727733 DOI: 10.1016/j.jhep.2012.06.014]

9 **Bruix J**, da Fonseca LG, Reig M. Insights into the success and failure of systemic therapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 617-630 [PMID: 31371809 DOI: 10.1038/s41575-019-0179-x]

10 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib *vs* sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

11 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]

12 **Heimbach JK**. Overview of the Updated AASLD Guidelines for the Management of HCC. *Gastroenterol Hepatol (N Y)* 2017; **13**: 751-753 [PMID: 29339953]

13 **Vogel A**, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, Nault JC, Neumann U, Ricke J, Sangro B, Schirmacher P, Verslype C, Zech CJ, Arnold D, Martinelli E; ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018; **29**: iv238-iv255 [PMID: 30285213 DOI: 10.1093/annonc/mdy308]

14 **Kudo M**. Systemic Therapy for Hepatocellular Carcinoma: Latest Advances. *Cancers (Basel)* 2018; **10** [PMID: 30380773 DOI: 10.3390/cancers10110412]

15 **Ding W**, Tan Y, Qian Y, Xue W, Wang Y, Jiang P, Xu X. First-line targ veted therapies of advanced hepatocellular carcinoma: A Bayesian network analysis of randomized controlled trials. *PLoS One* 2020; **15**: e0229492 [PMID: 32134981 DOI: 10.1371/journal.pone.0229492]

16 **Sonbol MB**, Riaz IB, Naqvi SAA, Almquist DR, Mina S, Almasri J, Shah S, Almader-Douglas D, Uson Junior PLS, Mahipal A, Ma WW, Jin Z, Mody K, Starr J, Borad MJ, Ahn DH, Murad MH, Bekaii-Saab T. Systemic Therapy and Sequencing Options in Advanced Hepatocellular Carcinoma: A Systematic Review and Network Meta-analysis. *JAMA Oncol* 2020; **6**: e204930 [PMID: 33090186 DOI: 10.1001/jamaoncol.2020.4930]

17 **Bi F**, Qin SK, Gu SZ, Bai YX, Chen ZD, Wang ZS, Ying J, Lu YY, Meng ZHQ, Pan HM, Yang P, Zhang HL, Chen X, Xu AB, Liu XF, Meng Q, Wu LQ, Chen F. Donafenib *vs* Sorafenib as first-line therapy in advanced hepatocellular carcinoma: an open-label, randomized, multicentre phase II/III trial. *J Clin Oncol* 2020; **38**: 4506-4506 [DOI: 10.1200/JCO.2020.38.15_suppl.4506]

18 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]

19 **Rücker G**. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012; **3**: 312-324 [PMID: 26053424 DOI: 10.1002/jrsm.1058]

20 **Rücker G**, Schwarzer G. Reduce dimension or reduce weights? *Stat Med* 2014; **33**: 4353-4369 [PMID: 24942211 DOI: 10.1002/sim.6236]

21 **Rücker G**, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015; **15**: 58 [PMID: 26227148 DOI: 10.1186/s12874-015-0060-8]

22 **Johnson PJ**, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters I, Cheng AL. Brivanib *vs* sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; **31**: 3517-3524 [PMID: 23980084 DOI: 10.1200/JCO.2012.48.4410]

23 **Yau T**, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, Kudo M, Han KH, Harding JJ, Merle P, Rosmorduc O, Wyrwicz L, Schott E, Choo SP, Kelley RK, Begic D, Chen G, Neely J, Anderson J, Sangro B. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) *vs* sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Ann Oncol* 2019; **30**: 874 [DOI: 10.1093/annonc/mdz394.029]

24 **Cainap C**, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens FA, Qian J, McKee MD, Ricker JL, Carlson DM, El-Nowiem S. Linifanib *vs* Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015; **33**: 172-179 [PMID: 25488963 DOI: 10.1200/JCO.2013.54.3298]

25 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

26 **Zhu AX**, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Carrilho FJ, Bruix J, Qin S, Thuluvath PJ, Llovet JM, Leberre MA, Jensen M, Meinhardt G, Kang YK. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2015; **33**: 559-566 [PMID: 25547503 DOI: 10.1200/JCO.2013.53.7746]

27 **Tak WY**, Ryoo BY, Lim HY, Kim DY, Okusaka T, Ikeda M, Hidaka H, Yeon JE, Mizukoshi E, Morimoto M, Lee MA, Yasui K, Kawaguchi Y, Heo J, Morita S, Kim TY, Furuse J, Katayama K, Aramaki T, Hara R, Kimura T, Nakamura O, Kudo M. Phase I/II study of first-line combination therapy with sorafenib plus resminostat, an oral HDAC inhibitor, *vs* sorafenib monotherapy for advanced hepatocellular carcinoma in east Asian patients. *Invest New Drugs* 2018; **36**: 1072-1084 [PMID: 30198057 DOI: 10.1007/s10637-018-0658-x]

28 **Cheng AL**, Kang YK, He AR, Lim HY, Ryoo BY, Hung CH, Sheen IS, Izumi N, Austin T, Wang Q, Greenberg J, Shiratori S, Beckman RA, Kudo M; Investigators' Study Group. Safety and efficacy of tigatuzumab plus sorafenib as first-line therapy in subjects with advanced hepatocellular carcinoma: A phase 2 randomized study. *J Hepatol* 2015; **63**: 896-904 [PMID: 26071796 DOI: 10.1016/j.jhep.2015.06.001]

29 **Cheng AL**, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzalone S, Yang L, Lechuga MJ, Raymond E. Sunitinib *vs* sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31**: 4067-4075 [PMID: 24081937 DOI: 10.1200/JCO.2012.45.8372]

30 **Yi M**, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer* 2019; **18**: 60 [PMID: 30925919 DOI: 10.1186/s12943-019-0974-6]

31 **Lee MS**, Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, Hack SP, Spahn J, Liu B, Abdullah H,

Wang Y, He AR, Lee KH; GO30140 investigators. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. *Lancet Oncol* 2020; **21**: 808-820 [PMID: 32502443 DOI: 10.1016/S1470-2045(20)30156-X]

32 **ten Doesschate T**, van Haren E, Wijma RA, Koch BCP. The effectiveness of nitrofurantoin, fosfomycin and trimethoprim for the treatment of cystitis in relation to renal function. *Clin Microbiol Infec* 2020; **26** [DOI: 10.1016/j.cmi.2020.03.001]

33 **Kudo M**, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, Takita M, Hagiwara S, Minami Y, Ida H, Takenaka M, Sakurai T, Watanabe T, Morita M, Ogawa C, Wada Y, Ikeda M, Ishii H, Izumi N, Nishida N. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. *Cancers (Basel)* 2019; **11** [PMID: 31370183 DOI: 10.3390/cancers11081084]

34 **Sun HC**, Zhu XD, Huang C, Shen YH, Ge NL, Chen Y, Tan CJ, Zhou J, Fan J. Combination therapy with lenvatinib and anti-PD-1 antibodies for unresectable or advanced hepatocellular carcinoma: A real-world study. *J Clin Oncol* 2020; **38**: e16610-e16610 [DOI: 10.1200/JCO.2020.38.15_suppl.e16610]

35 **Chen X**, Zhang Y, Zhang N, Ge Y, Jia W. Lenvatinib combined nivolumab injection followed by extended right hepatectomy is a feasible treatment for patients with massive hepatocellular carcinoma: a case report. *Onco Targets Ther* 2019; **12**: 7355-7359 [PMID: 31686845 DOI: 10.2147/OTT.S217123]

36 **He M**, Li Q, Zou R, Shen J, Fang W, Tan G, Zhou Y, Wu X, Xu L, Wei W, Le Y, Zhou Z, Zhao M, Guo Y, Guo R, Chen M, Shi M. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin *vs* Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. *JAMA Oncol* 2019; **5**: 953-960 [PMID: 31070690 DOI: 10.1001/jamaoncol.2019.0250]

37 **Park R**, Silva L, Nissaisorakarn V, Riano I, Saeed A. Comparison of systemic therapy efficacy in advanced hepatocellular carcinoma: Systematic review and frequentist network meta-analysis of randomized controlled trials. *J Clin Oncol* 2021; **39**: 293-293 [DOI: 10.1200/JCO.2021.39.3_suppl.293]

38 **Yamamoto Y**, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, Tohyama O, Semba T, Yamaguchi A, Hoshi SS, Mimura F, Haneda T, Fukuda Y, Kamata JI, Takahashi K, Matsukura M, Wakabayashi T, Asada M, Nomoto KI, Watanabe T, Dezso Z, Yoshimatsu K, Funahashi Y, Tsuruoka A. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* 2014; **6**: 18 [PMID: 25197551 DOI: 10.1186/2045-824X-6-18]

39 **Okamoto K**, Ikemori-Kawada M, Jestel A, von König K, Funahashi Y, Matsushima T, Tsuruoka A, Inoue A, Matsui J. Distinct binding mode of multikinase inhibitor lenvatinib revealed by biochemical characterization. *ACS Med Chem Lett* 2015; **6**: 89-94 [PMID: 25589937 DOI: 10.1021/mL500394m]

40 **Kato Y**, Tabata K, Kimura T, Yachie-Kinoshita A, Ozawa Y, Yamada K, Ito J, Tachino S, Hori Y, Matsuki M, Matsuoka Y, Ghosh S, Kitano H, Nomoto K, Matsui J, Funahashi Y. Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8+ T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. *PLoS One* 2019; **14**: e0212513 [PMID: 30811474 DOI: 10.1371/journal.pone.0212513]

41 **Zhang Q**, Liu H, Wang H, Lu M, Miao Y, Ding J, Li H, Gao X, Sun S, Zheng J. Lenvatinib promotes antitumor immunity by enhancing the tumor infiltration and activation of NK cells. *Am J Cancer Res* 2019; **9**: 1382-1395 [PMID: 31392076]

42 **Zhu RX**, Seto WK, Lai CL, Yuen MF. Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. *Gut Liver* 2016; **10**: 332-339 [PMID: 27114433 DOI: 10.5009/gnl15257]

43 **Fan JH**, Wang JB, Jiang Y, Xiang W, Liang H, Wei WQ, Qiao YL, Boffetta P. Attributable causes of liver cancer mortality and incidence in china. *Asian Pac J Cancer Prev* 2013; **14**: 7251-7256 [PMID: 24460283 DOI: 10.7314/apjcp.2013.14.12.7251]

44 **Casadei Gardini A**, Puzzoni M, Montagnani F, Marisi G, Tamburini E, Cucchetti A, Solaini L, Foschi FG, Conti F, Ercolani G, Cascinu S, Scartozzi M. Profile of lenvatinib in the treatment of hepatocellular carcinoma: design, development, potential place in therapy and network meta-analysis of hepatitis B and hepatitis C in all Phase III trials. *Onco Targets Ther* 2019; **12**: 2981-2988 [PMID: 31118665 DOI: 10.2147/OTT.S192572]

45 **Park J**, Cho J, Lim JH, Lee MH, Kim J. Relative Efficacy of Systemic Treatments for Patients with Advanced Hepatocellular Carcinoma According to Viral Status: A Systematic Review and Network Meta-Analysis. *Target Oncol* 2019; **14**: 395-403 [PMID: 31290003 DOI: 10.1007/s11523-019-00651-7]

46 **Department of Medical Administration**, National Health and Health Commission of the People's Republic of China. [Guidelines for diagnosis and treatment of primary liver cancer in China (2019 edition)]. *Zhonghua Gan Zang Bing Za Zhi* 2020; **28**: 112-128 [PMID: 32164061 DOI: 10.3760/cma.j.issn.1007-3418.2020.02.004]

47 **Yen CJ**, Kim TY, Feng YH, Chao Y, Lin DY, Ryoo BY, Huang DC, Schnell D, Hocke J, Loembé AB, Cheng AL. A Phase I/Randomized Phase II Study to Evaluate the Safety, Pharmacokinetics, and Efficacy of Nintedanib *vs* Sorafenib in Asian Patients with Advanced Hepatocellular Carcinoma. *Liver Cancer* 2018; **7**: 165-178 [PMID: 29888206 DOI: 10.1159/000486460]

48 **Ciuleanu T**, Bazin I, Lungulescu D, Miron L, Bondarenko I, Deptala A, Rodriguez-Torres M, Giantonio B, Fox NL, Wissel P, Egger J, Ding M, Kalyani RN, Humphreys R, Gribbin M, Sun W. A

randomized, double-blind, placebo-controlled phase II study to assess the efficacy and safety of mapatumumab with sorafenib in patients with advanced hepatocellular carcinoma. *Ann Oncol* 2016; **27**: 680-687 [PMID: 26802147 DOI: 10.1093/annonc/mdw004]

49 **Abou-Alfa GK**, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB. Doxorubicin plus sorafenib *vs* doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA* 2010; **304**: 2154-2160 [PMID: 21081728 DOI: 10.1001/jama.2010.1672]

50 **Cheng AL**, Thongprasert S, Lim HY, Sukeepaisarnjaroen W, Yang TS, Wu CC, Chao Y, Chan SL, Kudo M, Ikeda M, Kang YK, Pan H, Numata K, Han G, Balsara B, Zhang Y, Rodriguez AM, Wang Y, Poon RT. Randomized, open-label phase 2 study comparing frontline dovitinib *vs* sorafenib in patients with advanced hepatocellular carcinoma. *Hepatology* 2016; **64**: 774-784 [PMID: 27082062 DOI: 10.1002/hep.28600]

51 **Hsu C**, Yang TS, Huo TI, Hsieh RK, Yu CW, Hwang WS, Hsieh TY, Huang WT, Chao Y, Meng R, Cheng AL. Vandetanib in patients with inoperable hepatocellular carcinoma: a phase II, randomized, double-blind, placebo-controlled study. *J Hepatol* 2012; **56**: 1097-1103 [PMID: 22245891 DOI: 10.1016/j.jhep.2011.12.013]

52 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

53 **Palmer DH**, Ma YT, Peck-Radosavljevic M, Ross P, Graham J, Fartoux L, Deptala A, Studeny M, Schnell D, Hocke J, Loembé AB, Meyer T. A multicentre, open-label, phase-I/randomised phase-II study to evaluate safety, pharmacokinetics, and efficacy of nintedanib vs. sorafenib in European patients with advanced hepatocellular carcinoma. *Br J Cancer* 2018; **118**: 1162-1168 [PMID: 29563636 DOI: 10.1038/s41416-018-0051-8]

54 **Thomas MB**, Garrett-Mayer E, Anis M, Anderton K, Bentz T, Edwards A, Brisendine A, Weiss G, Siegel AB, Bendell J, Baron A, Duddalwar V, El-Khoueiry A. A Randomized Phase II Open-Label Multi-Institution Study of the Combination of Bevacizumab and Erlotinib Compared to Sorafenib in the First-Line Treatment of Patients with Advanced Hepatocellular Carcinoma. *Oncology* 2018; **94**: 329-339 [PMID: 29719302 DOI: 10.1159/000485384]

55 **Abou-Alfa GK**, Shi Q, Knox JJ, Kaubisch A, Niedzwiecki D, Posey J, Tan BR Jr, Kavan P, Goel R, Lammers PE, Bekaii-Saab TS, Tam VC, Rajdev L, Kelley RK, El Dika I, Zemla T, Potaracke RI, Balletti J, El-Khoueiry AB, Harding JH, Suga JM, Schwartz LH, Goldberg RM, Bertagnolli MM, Meyerhardt J, O'Reilly EM, Venook AP. Assessment of Treatment With Sorafenib Plus Doxorubicin *vs* Sorafenib Alone in Patients With Advanced Hepatocellular Carcinoma: Phase 3 CALGB 80802 Randomized Clinical Trial. *JAMA Oncol* 2019 [PMID: 31486832 DOI: 10.1001/jamaoncol.2019.2792]

56 **Jouve JL**, Lecomte T, Bouché O, Barbier E, Khemissa Akouz F, Riachi G, Nguyen Khac E, Ollivier-Hourmand I, Debette-Gratien M, Faroux R, Villing AL, Vergniol J, Ramee JF, Bronowicki JP, Seitz JF, Legoux JL, Denis J, Manfredi S, Phelip JM; PRODIGE-11 investigators/collaborators. Pravastatin combination with sorafenib does not improve survival in advanced hepatocellular carcinoma. *J Hepatol* 2019; **71**: 516-522 [PMID: 31125576 DOI: 10.1016/j.jhep.2019.04.021]

57 **Lee FA**, Zee BC, Cheung FY, Kwong P, Chiang CL, Leung KC, Siu SW, Lee C, Lai M, Kwok C, Chong M, Jolivet J, Tung S. Randomized Phase II Study of the X-linked Inhibitor of Apoptosis (XIAP) Antisense AEG35156 in Combination With Sorafenib in Patients With Advanced Hepatocellular Carcinoma (HCC). *Am J Clin Oncol* 2016; **39**: 609-613 [PMID: 24977690 DOI: 10.1097/coc.0000000000000099]

58 **Assenat E**, Pageaux GP, Thézenas S, Peron JM, Bécouarn Y, Seitz JF, Merle P, Blanc JF, Bouché O, Ramdani M, Poujol S, de Forges H, Ychou M, Boige V. Sorafenib alone vs. sorafenib plus GEMOX as 1st-line treatment for advanced HCC: the phase II randomised PRODIGE 10 trial. *Br J Cancer* 2019; **120**: 896-902 [PMID: 30944458 DOI: 10.1038/s41416-019-0443-4]

59 **Azim HA**, Omar A, Atef H, Zawahry H, Shaker MK, Abdelmaksoud AK, EzzElarab M, Abdel-Rahman O, Ismail M, Kassem L, Waked I. Sorafenib plus tegafur-uracil (UFT) *vs* sorafenib as first line systemic treatment for patients with advanced stage HCC: a Phase II trial (ESLC01 study). *J Hepatocell Carcinoma* 2018; **5**: 109-119 [PMID: 30510922 DOI: 10.2147/JHC.S169285]

60 **Koeberle D**, Dufour JF, Demeter G, Li Q, Ribi K, Samaras P, Saletti P, Roth AD, Horber D, Buehlmann M, Wagner AD, Montemurro M, Lakatos G, Feilchenfeldt J, Peck-Radosavljevic M, Rauch D, Tschanz B, Bodoky G; Swiss Group for Clinical Cancer Research (SAKK). Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29). *Ann Oncol* 2016; **27**: 856-861 [PMID: 26884590 DOI: 10.1093/annonc/mdw054]

61 **Qin S**, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, Yang TS, Bhudhisawasdi V, Kang WK, Zhou Y, Lee JH, Sun Y. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/Leucovorin *vs* doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol* 2013; **31**: 3501-3508 [PMID: 23980077 DOI: 10.1200/JCO.2012.44.5643]

62 **Yeo W**, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, Koh J, Mo FK, Yu SC, Chan AT, Hui P, Ma B, Lam KC, Ho WM, Wong HT, Tang A, Johnson PJ. A randomized phase III study of doxorubicin

vs cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005; **97**: 1532-1538 [PMID: 16234567 DOI: 10.1093/jnci/dji315]

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