

# Systematic literature review of trials assessing recommended systemic treatments in hepatocellular carcinoma

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**Aim:** To identify and evaluate the similarity of all trials assessing recommended treatments for advanced hepatocellular carcinoma. **Materials & methods:** Single arm and randomized trials from any phase and published any time up to February 2021 were systematically searched. **Results:** From 5677 records reviewed, 50 trials were included in the review, and 24 for assessed for similarity. In the first-line (1L) setting, several trials assessing sorafenib were noted for enrolling patients with more severe disease and/or performance status than other 1L trials; trials within the second-line (2L) setting were generally similar. Median survival was <2 years in all trial arms. **Conclusions:** Trials assessing recommended treatments are largely similar and appropriate for quantitative comparisons of several efficacy and safety outcomes.

**Lay abstract:** Several drugs are recommended for patients with advanced hepatocellular carcinoma (HCC). We reviewed all the trials that tested these drugs. Most trials had similar design and patient criteria, except some of the early trials for sorafenib allowed patients with more severe disease. We examined the median overall survival from trials where patients were randomized to receive an active drug or a non-active drug (placebo). Patients getting their first HCC drug survived 4.0–19.2 months (active drug) or 3.5–7.9 months (placebo). Patients getting their second HCC drug survived 8.5–13.9 months (active drug) or 7.3–10.6 months (placebo). Nearly one in seven patients stopped participating in a drug trial due to adverse events. This review summarizes the clinical potential and unmet needs in drugs to treat patients with advanced HCC.

First draft submitted: 30 March 2021; Accepted for publication: 3 August 2021; Published online: 26 August 2021

**Keywords:** BCLC stage • ECOG performance status • hepatocellular carcinoma • immuno-oncology agent • similarity assessment • systemic treatment

With approximately 841,000 new liver cancer cases and approximately 781,000 liver cancer deaths globally in 2018, liver cancer is the sixth most common form of cancer and the fourth most common cause among all cancer deaths [1]. The nearly equal rates of overall incidence and mortality indicate the poor prognosis associated with liver cancer. Cases have increased 75% since 1990, mostly due to population increases and changes in age distributions [2]. Incidence and mortality are highest in Asia and Africa, and the age-standardized incidence and mortality of liver cancer is over two-times higher among men than women [1]. Based on age and sex, age-standardized rates of liver cancer incidence are highest in men aged 60 years and older, increasing globally from 68 per 100,000 in 1990 to 87 per 100,000 in 2017 [3].

Hepatocellular carcinoma (HCC) accounts for 75–85% of all liver cancers [4]; therefore, HCC is a primary cause of cancer-related burden and deaths. Major risk factors in the development of HCC include cirrhosis, which may be due to infection with hepatitis B or C, alcohol abuse, non-alcoholic fatty liver disease (NAFLD), genetic hemochromatosis, primary biliary cholangitis, or other factors [5]. Globally, liver cancer deaths are mostly due to three risk factors: alcohol use (30%), hepatitis B (33%), and hepatitis C (21%) [2]. The incidence of these etiologies

varies dramatically across regions, with alcohol and hepatitis C being more prominent in the US and hepatitis B being more prominent in East Asia [2].

A variety of staging systems are available to describe HCC. The staging system recommended by guidelines from USA and Europe is the Barcelona Clinic Liver Cancer (BCLC) system [6] due to the system's assessment of tumor burden, liver function, patient performance status and validation across global populations [5,7]. The BCLC staging system is the only system meeting all evidence-based criteria for the assessment of prognosis [5]. The BCLC stages of 0, A, B, C and D represent the spectrum of very early stage to terminal-stage patients, respectively. The BCLC staging system includes measurements of patients' physical function, as measured by the Eastern Cooperative Oncology Group (ECOG) performance status [8], liver function, as measured by the Child–Pugh class [9,10], and tumor burden, as measured by tumor, node, metastasis (TNM).

Approximately a third of patients with HCC are diagnosed with advanced disease [11], when surgical and locoregional treatments are no longer feasible or effective. For these patients, the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines<sup>®</sup>) recommend systemically administered treatments (i.e., atezolizumab + bevacizumab, lenvatinib, nivolumab, sorafenib, or FOLFOX in the first-line [1L] setting, and cabozantinib, lenvatinib, nivolumab ± ipilimumab, pembrolizumab [to be considered for microsatellite instability-high HCC], ramucirumab, regorafenib, or sorafenib in the second-line [2L] setting, following disease progression) [12]; these treatments are typically indicated only for patients who have preserved liver function (i.e., Child–Pugh A) and good performance status (i.e., ECOG 0-1).

The clinical trials assessing recommended treatments are typically performed as single-arm trials or as randomized controlled trials (RCTs) comparing against placebo, best supportive care (BSC), or another recommended treatment. The comparative efficacy and safety of various systemic treatments for HCC have been indirectly assessed using network meta-analysis (NMA) [13–15].

NMAs require performing a thorough qualitative assessment of trial, patient, treatment, and outcome characteristics before analysis to ensure the comparability of trials and validity of findings [16]. Recent NMAs have compared various treatments used in 1L or 2L settings, but not all have documented similarity assessments of both design and patient characteristics. Furthermore, many NMAs included treatments irrespective of whether they were recommended in major guidelines. Last, single-arm trials of systemic treatments for HCC, which may be comparable via matching adjusted indirect comparisons [17,18], are seldom qualitatively reviewed in aggregate for similarity.

In summary, recent meta-analyses of systemic treatments used in HCC have not uniformly reported formal feasibility assessments and have not included treatments that align with current recommendations from the NCCN Guidelines. The objectives of this study were to identify all clinical trials that evaluated treatments recommended by the NCCN Guidelines in patients with advanced HCC, assess the similarity of their design and patient populations, and determine whether these trials were sufficiently similar for future quantitative comparisons, particularly using NMA approaches.

## Materials & methods

Methods employed in this systematic literature review (SLR) were specified in advance and documented in a study protocol. This review was not registered. Reporting of the SLR was guided by the PRISMA 2020 statement [19].

### Literature Search

Studies of interest to this SLR included RCTs and single-arm trials investigating the efficacy and safety of treatments recommended by the NCCN Guidelines for HCC in the 1L or 2L setting (Supplementary Table 1). A systematic search was conducted on 12 February 2021 (Supplementary Table 2). Data sources included MEDLINE (1946–present), Embase (1947–present), the Cochrane Database of Systematic Reviews, ClinicalTrials.gov, the EU Clinical Trials Register, and conference abstracts from the American Association for the Study of Liver Diseases Liver Meeting, American Society of Clinical Oncology Annual Meeting, European Association for the Study of Liver International Liver Congress, European Society for Medical Oncology Congress, European Society for Medical Oncology Asia Congress, and Gastrointestinal Cancers Symposium 2016–2021 conferences. Results of all literature searches were compiled into a Microsoft Excel spreadsheet, and all eligible articles were screened by two independent reviewers. At each screening step, trial inclusion and exclusion were based on predefined selection criteria, first at the title and abstract level, and then as full texts. For any trials represented in both an article and a conference abstract and/or trial registry, the article was considered the main record, and the conference abstract or registry was considered a

duplicate. Trials were excluded if the intervention combined a recommended treatment with a non-recommended treatment or combined two treatments currently recommended only as monotherapies.

After all relevant publications were identified, two independent reviewers extracted data from the articles and reconciled any discrepancies. A third independent reviewer was consulted as necessary and adjudicated where consensus could not be reached. A full list of variables extracted is provided in [Supplementary Table 3](#).

### Risk of bias

Criteria from the Centre for Reviews and Dissemination were used for assessment of the risk of bias in RCTs; the Newcastle–Ottawa Scale with modifications for cohort studies was used for single-arm studies [20,21]. The risk of bias assessment was conducted at the study level by two blinded reviewers and adjudicated by a third independent reviewer if necessary.

### Similarity assessment

A qualitative similarity assessment was performed on all RCTs that compared at least two interventions of interest or placebo and any single-arm trials. Studies were first characterized as 1L or 2L based on trial inclusion criteria, then as single arm or RCTs, and finally by the drug class of the treatment used. Drug classes include tyrosine kinase inhibitors (TKI; i.e., lenvatinib, sorafenib), vascular endothelial growth factor receptor inhibitors (VEGFRI; i.e., bevacizumab, cabozantinib, ramucirumab, regorafenib), immuno-oncology agents (IO; i.e., atezolizumab, ipilimumab, nivolumab, pembrolizumab) or none (i.e., placebo, BSC). Trial inclusion/exclusion criteria were compared for the following characteristics (if described): BCLC stage or other tumor stages, ECOG performance status, Child–Pugh class, hepatic encephalopathy, ascites, bleeding risk, time since loco-regional treatment, and any excluded viral infections. Patient and disease characteristics assessed for similarity included mean or median age, proportion male, the proportion from the Asia–Pacific region, vascular invasion, extrahepatic spread, hepatitis B, hepatitis C, AFP, ECOG performance status, BCLC stage and Child–Pugh class. Efficacy and safety outcomes of interest were also reviewed. All proportions were converted to percentages for presentation. Missing data were reported as ‘not reported’. Figures were made for patient characteristics (bubble charts), hepatitis prevalence–geographic region and disease severity–survival relationships (scatter plots), within-trial survival comparisons (bar charts), and disease stage/severity, survival, tumor response, and safety (histograms). As this study was intended to provide a qualitative review, median values and ranges were presented for survival outcomes, tumor response and safety outcomes.

### Results

The literature search identified a total of 5677 records to be screened ([Supplementary Figure 1](#)). Of these, 455 were duplicates between sources and 5148 were excluded upon title/abstract review. The primary reasons for exclusion at this stage included study designs not of interest (e.g., observational studies, reviews; 3121 records) and populations not of interest (e.g., patients with HCC who were receiving loco-regional treatment, populations including a mix of cancer types; 821 records). The full texts of the remaining 74 records were reviewed, and 17 records were excluded at this stage (SLRs, 9 records; comparators not of interest, 5 records [22–26]; outcomes not of interest, 1 record [27]; duplicates, 1 record [28]; study design not of interest, 1 record [29]). Finally, 57 records (representing 50 trials) were included in the SLR. These 50 trials included 34 trials in the 1L setting (six single arm [30–35], six RCTs comparing against a recommended treatment or placebo [36–43], one trial with both single arm and randomized groups [44], and 26 RCTs comparing against a non-recommended treatment [45–70]) and 11 trials in the 2L setting (five single arm [71–76], five RCTs comparing against placebo [77–82], and one trial with both single arm and randomized groups [83–86]).

Of these 50 trials, all single-arm trials and any RCTs that compared a recommended treatment against a second recommended treatment or placebo were further examined for similarity; therefore, the similarity assessment included 24 trials (13 1L trials and 11 2L trials; [Table 1](#)). The two trials with both single arm and randomized groups were included in the similarity assessment, despite the fact that the randomized groups in these trials do not include two recommended treatment arms. Conversely, the 26 RCTs comparing a recommended treatment against non-recommended treatments (sorafenib, 25 trials; FOLFOX, one trial; [Supplementary Table 4](#)) were not examined for similarity. Risk of bias for the studies included in the similarity assessment can be found in [Supplementary Table 5–8](#).

Table 1. Trials included in the similarity assessment.

Drug class	Study (year)	Trial acronym	NCT	Intervention	ITT (n)	Ref.
<b>1L, single arm or dose finding</b>						
TKI	Abou-Alfa (2006)	NR	NCT00044512	Sorafenib	137	[30]
	Furuse (2008)	NR	NR	Sorafenib	14	[31]
	Yau (2009)	NR	NR	Sorafenib	51	[32]
	Hidaka (2015)	NR	NR	Sorafenib	37	[33]
	Ikeda (2017)	NR	NCT00946153	Lenvatinib	46	[34]
	Suzuki (2018)	NR	NR	Sorafenib	52	[35]
<b>1L, RCT with 2 comparators of interest</b>						
TKI vs none	Llovet (2008)	SHARP	NCT00105443	Sorafenib Placebo	292 303	[36]
	Cheng (2009)	Sorafenib AP	NCT00492752	Sorafenib Placebo	150 76	[37]
	Ji (2014)	NR	NR	Sorafenib BSC	95 94	[38]
TKI vs TKI	Kudo (2018)	REFLECT	NCT01761266	Lenvatinib Sorafenib	478 476	[39]
IO vs TKI	Yau (2019a) Bristol-Myers Squibb†	CheckMate 459	NCT02576509	Nivolumab Sorafenib	371 372	[40,41]
IO + VEGFRI vs TKI	Finn (2020b) Finn (2021†)	IMbrave150	NCT03434379	Atezolizumab + bevacizumab Sorafenib	336 165	[42,43]
<b>1L, single arm and RCT</b>						
IO + VEGFRI	Lee (2020)	GO30140	NCT02715531	Atezolizumab + bevacizumab (group A)	104	[44]
IO + VEGFRI vs IO				Atezolizumab + bevacizumab xs (group F)	60	
				Atezolizumab (group F)	59	
<b>2L, single arm or dose finding</b>						
TKI	Ikeda (2016)	NR	NR	Lenvatinib	20	[71]
	Kudo (2021)	NR	NCT03586973	Cabozantinib	34	[72]
VEGFRI	Bruix (2013)	NR	NCT01003015	Regorafenib	36	[73]
IO	Zhu (2018) Kudo (2020†)	KEYNOTE 224	NCT02702414	Pembrolizumab	104	[74,75]
	Feun (2019)	NR	NCT02658019	Pembrolizumab	28	[76]
<b>2L, RCT with 2 comparators of interest</b>						
TKI vs none	Abou-Alfa (2018)	CELESTIAL	NCT01908426	Cabozantinib	470	[77]
				Placebo	237	
VEGFRI vs none	Zhu (2015)	REACH	NCT01140347	Ramucirumab Placebo	283 282	[78]
	Bruix (2017)	RESORCE	NCT01774344	Regorafenib Placebo	379 194	[79]
	Zhu (2019)	REACH-2	NCT02435433	Ramucirumab Placebo	197 95	[80]
IO vs none	Finn (2020c) Merle (2021†)	KEYNOTE 240	NCT02702401	Pembrolizumab Placebo	278 135	[81,82]
<b>2L, single arm and RCT</b>						
IO	El-Khoueiry (2017)	CheckMate 040	NCT01658878	Nivolumab‡	262	[83]
IO + IO	Yau (2020a) El-Khoueiry (2021†)			Nivolumab + ipilimumab§	148	[84,85]
IO + VEGFRI vs IO + VEGFRI + IO	Yau (2020b)			Nivolumab + cabozantinib	36	[86]
				Nivolumab + cabozantinib + ipilimumab	35	

Trials are arranged by 1L or 2L, single arm or RCT, drug class, and publication year.

†Secondary publication.

‡Includes 'dose escalation' and 'dose expansion' cohorts.

§Includes different doses and schedules labeled by authors as 'A', 'B' and 'C'.

1L: First line; 2L: Second line; BSC: Best supportive care; IO: Immuno-oncology agent; NCT: Clinicaltrials.gov identifier; NR: Not reported; RCT: Randomized controlled trial; TKI: Tyrosine kinase inhibitor; VEGFRI: Vascular endothelial growth factor receptor inhibitor.

### Design & inclusion criteria

Trial design and inclusion criteria were reviewed first for similarity. In terms of study design (Supplementary Table 9), blinding varied among the RCTs; most of the 1L RCTs were open label, but all the 2L RCTs were double blind. The majority of trials (18 of 24) were Phase II or Phase III, and half the trials (12 of 24) were global (i.e., included patients from countries within and not within the Asia–Pacific region); however, three trials included patients from outside Asia–Pacific countries [30,36,76] and nine trials included patients exclusively from Asia–Pacific countries [31–35,37,38,71,72]. Nine of the 12 global trials (i.e., CELESTIAL, CheckMate 040, GO30140, IMbrave150, KEYNOTE-240, REFLECT, REACH, REACH-2, RESORCE) provided subgroup analyses for patients from the Asia–Pacific region in the original publication or in separate analyses [87–94].

Inclusion criteria for general disease characteristics, such as the ECOG performance status, BCLC stage, and Child–Pugh class, were largely similar within the trials (Supplementary Table 10); however, some studies allowed patients with more advanced disease stage to enroll. These included four trials that allowed patients with ECOG performance status of 2 to enroll (including early trials for sorafenib) [35–38] and six trials that allowed patients with Child–Pugh class B to enroll [30,31,35,38,44,76]. Notably, all 2L RCTs had highly similar general inclusion criteria regarding ECOG performance status of 0 or 1, BCLC stage B or C, and Child–Pugh class A; patients with more severe disease were excluded from 2L RCTs. The time since loco-regional treatment was at least 4 weeks for any study mentioning this criterion. Specific disease characteristics assessed included hepatic encephalopathy, ascites, and bleeding risk; these criteria were either not reported or not allowed within varying timeframes of randomization or treatment initiation. Excluded viral infections were also mostly similar, with a co-infection of hepatitis B and C being the only hepatitis condition not allowed (Supplementary Table 11). In the 1L setting, up to 90% of patients had hepatitis B and 79% of patients had hepatitis C; the maximum proportions were lower in the 2L setting (56 and 45%, respectively). Most of the trials assessing patients in the 2L setting required that the only prior treatment was sorafenib; several required that no prior IO treatments had been administered (Supplementary Table 12).

### Patient & disease characteristics

Minimum and maximum values for each trial arm are used to describe the demographic and disease characteristics shown in Figure 1. Patient age and sex were fairly consistent between studies, with single-arm trials and RCTs in 1L and 2L settings enrolling patients aged 59–68 years (mean) or 51–73 years (median); 71–93% of patients were male. The proportion of patients from the Asia–Pacific region varied widely. Trials included a wide range of patients with vascular invasion (0–88%) and extrahepatic spread (21–86%).

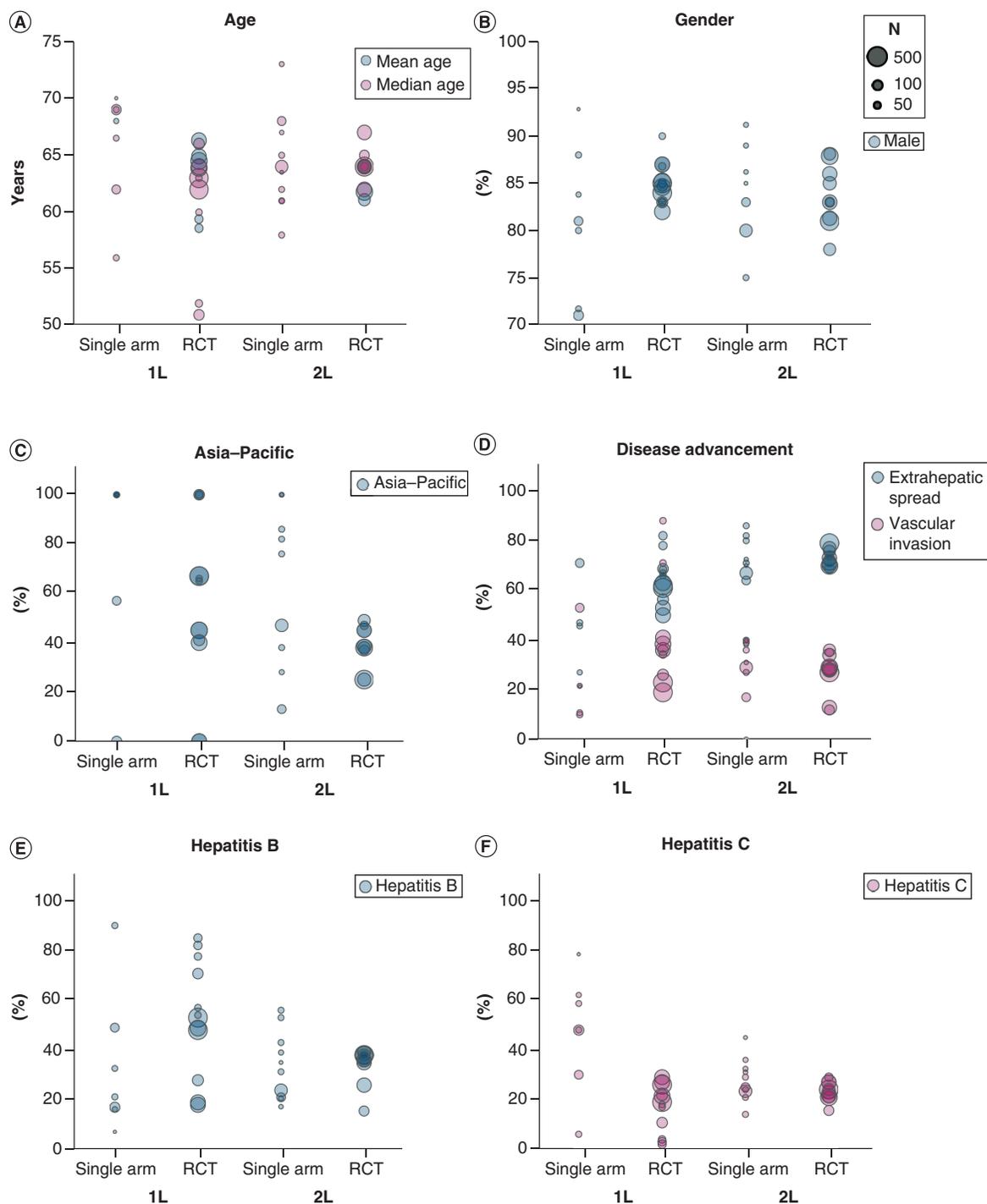
There appeared to be a relationship between the proportion of patients enrolled from Asia–Pacific versus the prevalence of hepatitis B, but not the prevalence of hepatitis C (Supplementary Figure 2), which was expected given the regional epidemiology of hepatitis B [95].

Reporting of AFP was heterogeneous, hindering the review of similarity; three trials reported the proportion of patients with AFP  $\geq 200$  ng/ml [34,74,81]; nine trials reported the proportion of patients with AFP  $\geq 400$  ng/ml [32,42,44,72,76–79,83]; six reported mean or median values for the cohort [33,36,39,71,78,80]; two reported only the proportion with levels greater than the upper limit of detection [30,37]; six trials provided no indication of AFP [31,35,38,40,73,86]. Two studies required AFP  $> 400$  ng/ml for inclusion [76,80]. Therefore it is not possible to state the similarity of AFP levels across all trials.

### Performance status & disease stage

The ECOG performance status, BCLC stage, and Child–Pugh class of patients from each trial arm were also examined for similarity. The ranges of enrolled patients who were ECOG 0 (i.e., fully active), ECOG 1 (i.e., able to perform light/sedentary activity) and ECOG 2 (i.e., unable to perform work activities but capable of self-care) were 25–100%, 17–75% and 0–8%, respectively, in the 1L setting (Figure 2). Notably, two of the early RCTs assessing sorafenib [37,38] enrolled a much lower proportion of patients who were ECOG 0 compared with other 1L single arm trials and RCTs; these two trials also enrolled patients who were ECOG 2. Aside from these two trials [37,38], the ECOG performance status of patients in 1L trials was largely similar. In the 2L setting, the ranges of enrolled patients who were ECOG 0 and 1 were 52–91% and 9–48%, respectively, and appeared broadly similar.

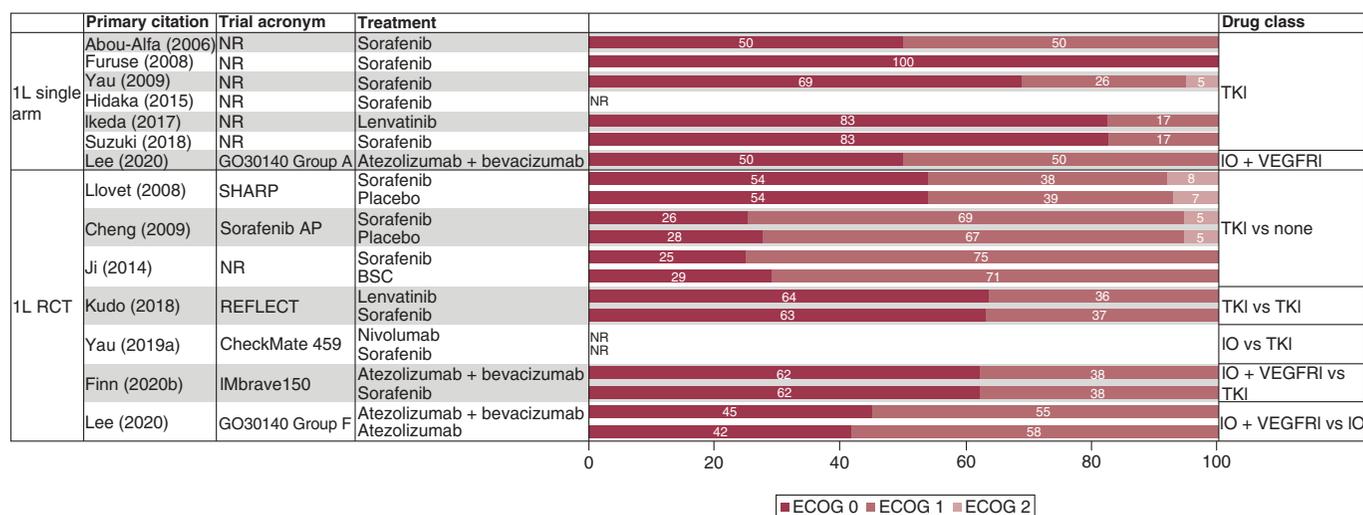
Seventeen of the 24 trials in the similarity assessment reported patients' BCLC stage at baseline. Patients staged BCLC C (i.e., advanced disease) ranged 43–96% in the 1L setting (Supplementary Figure 4). Two trials in the 1L single-arm setting had a lower proportion of BCLC C patients than most other 1L trials, while the Sorafenib AP trial enrolled BCLC C patients almost exclusively [33,35,37]. Aside from these three trials, the BCLC staging



**Figure 1. Patient characteristics.** Markers indicate patient characteristics from each trial arm. The bubble size indicates the size of the ITT population. (A) Mean or median age. (B) Proportion male. (C) Proportion from the Asia-Pacific region (global studies). (D) Prevalence of extrahepatic spread and vascular invasion. (E) Prevalence of hepatitis B. (F) Prevalence of hepatitis C. 1L: First line; 2L: Second line; ITT: Intent to treat; RCT: Randomized controlled trial.

appeared broadly similar in the 1L setting. In the 2L setting, BCLC C patients composed 76%–94% of patients; in this regard, 2L trials appeared broadly similar.

Patients with a Child–Pugh score of 5–6 (i.e., Child–Pugh A, considered well-compensated) varied throughout the trial arms, ranging 43–100% in the 1L setting (Supplementary Figure 5). Four of the seven 1L single-arm trials



**Figure 2. ECOG performance status in first-line trials.**

1L: First line; BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; IO: Immuno-oncology agent; NR: Not reported; RCT: Randomized controlled trial; TKI: Tyrosine kinase inhibitor; VEGFRI: Vascular endothelial growth factor receptor inhibitor.

enrolled >20% Child–Pugh B patients [30–32,35]. One 1L RCT [38] enrolled only Child–Pugh B or C patients; other 1L RCTs enrolled <10% Child–Pugh B patients and were therefore considered similar in Child–Pugh class. In the 2L setting, one trial enrolled 55% Child–Pugh B patients [71]; all other 2L trials enrolled >90% Child–Pugh A patients and were considered similar.

In summary, some trials in the 1L setting included patients who had more advanced disease based on ECOG performance status [30,37,38], BCLC stage [37], and Child–Pugh class [30–32,35,38]. All these trials assessed sorafenib as single arm or placebo-controlled RCTs. Patients in 2L trials were more similar in terms of these characteristics, aside from one single-arm trial for lenvatinib [71].

## Efficacy results

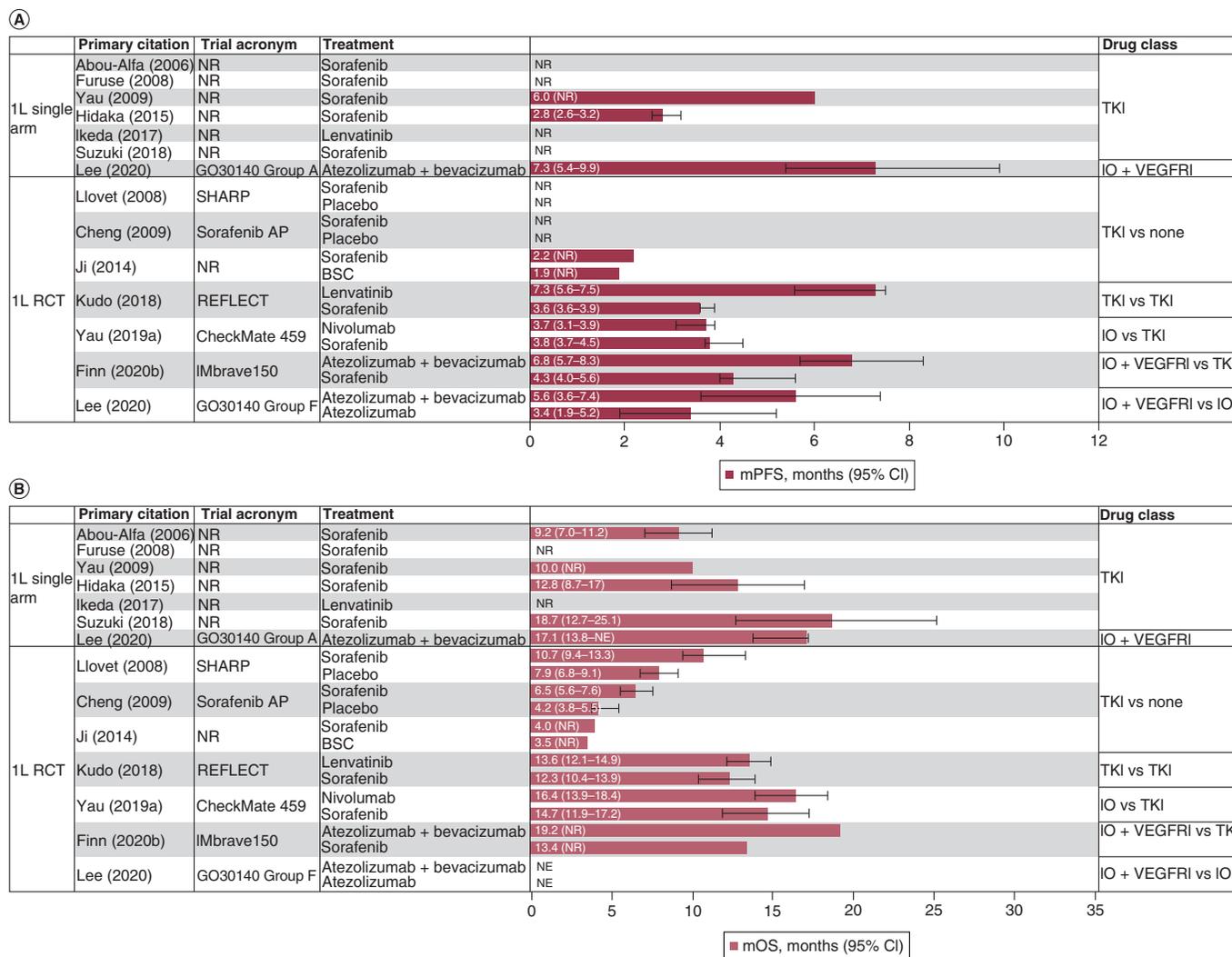
### Survival

The median overall survival (mOS) ranged from 3.5 to 19.2 months in the 1L setting and 7.3 to 22.2 months in the 2L setting. In 1L RCTs, the median (range) of mOS values was 13.4 (4.0–19.2) months in active treatment arms and 4.2 (3.5–7.9) months in placebo/BSC arms (Figure 3); in 2L RCTs, the median (range) of mOS values was 10.2 (8.5–13.9) months in active treatment arms and 7.8 (7.3–10.6) months in placebo arms (Supplementary Figure 6).

The median progression-free survival (mPFS) ranged 1.9–7.3 months in the 1L setting and 1.5–6.8 months in the 2L setting. In 1L RCTs, the median (range) of mPFS values was 3.8 (2.2–7.3) months in active treatment arms and 1.9 months in BSC (Figure 3); in 2L RCTs, the median (range) of mPFS values was 3.3 (2.8–6.8) months in active treatment arms and 1.9 (1.5–2.8) months in placebo arms (Supplementary Figure 6).

The association between disease advancement and survival in the 1L setting was explored by plotting the proportion of ECOG 0 patients, BCLC B patients and Child–Pugh A patients versus the mOS for the trials reporting both these outcomes (Supplementary Figure 9). Based on qualitative review, the differences in mOS observed in 1L trials may be partially correlated with the underlying ECOG performance status of patients enrolled.

The 1L and 2L RCTs also reported the hazard ratio (HR) and 95% confidence interval (CI) of survival based on the Kaplan–Meier curves of PFS and OS. In the 1L setting, all trials assessing sorafenib versus placebo/BSC found a significant improvement in both PFS and OS in favor of sorafenib [36–38]. Similarly, the combination of atezolizumab + bevacizumab was associated with an improvement in PFS and OS versus sorafenib [42,43]. The trial assessing lenvatinib and sorafenib demonstrated lenvatinib's non-inferiority [39], while the comparison of nivolumab versus sorafenib did not show a significant improvement in either outcome [40]. Last, the comparison of atezolizumab + bevacizumab versus atezolizumab alone found an improvement in PFS, but OS was not reported



**Figure 3. Median survival in first-line trials. (A) mPFS. (B) mOS.**

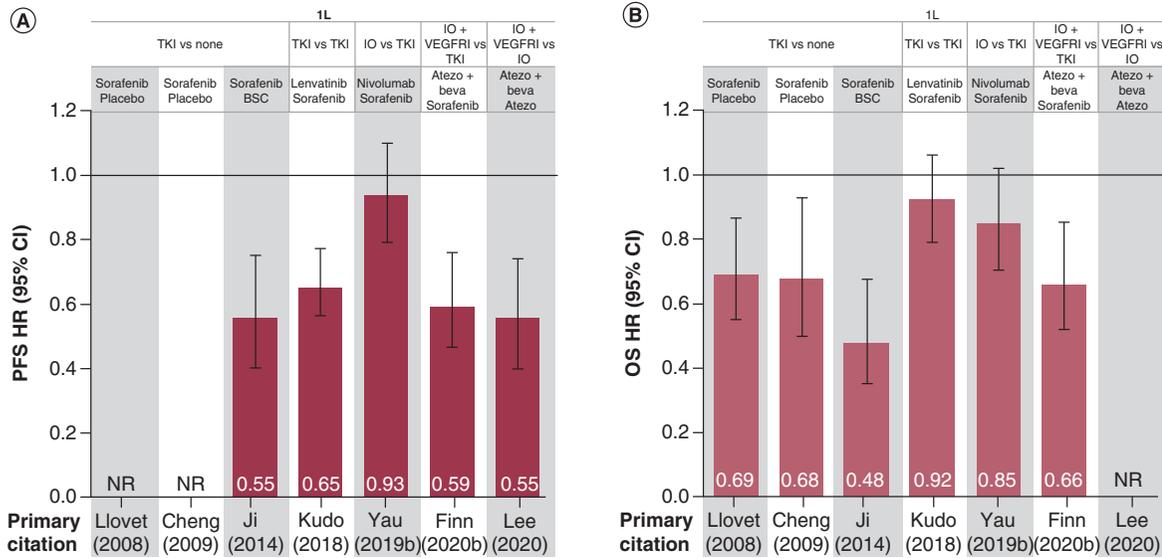
1L: First line; BSC: Best supportive care; IO: Immuno-oncology agent; NE: Not evaluable; NR: Not reported; mOS: Median overall survival; mPFS: Median progression-free survival; RCT: Randomized controlled trial; TKI: Tyrosine kinase inhibitor; VEGFRI: Vascular endothelial growth factor receptor inhibitor.

(Figure 4) [44]. In the 2L setting, cabozantinib and regorafenib were associated with significant improvements in PFS and OS over placebo [77,79]; results for ramucirumab were mixed [78,80], and pembrolizumab did not significantly lower PFS and OS per the trial’s specified criteria [81,82] (Supplementary Figure 7).

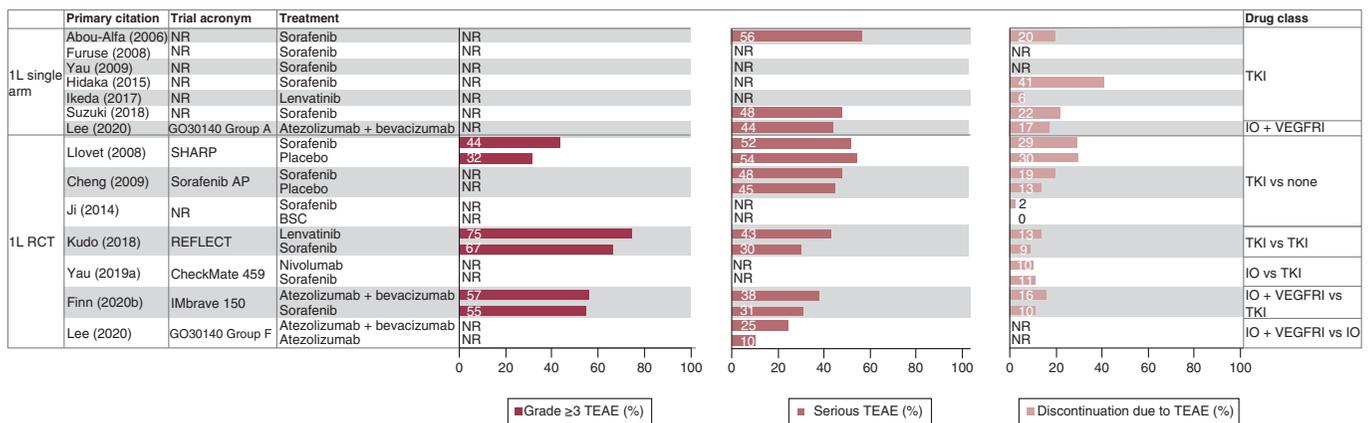
Other time-to-event outcomes, such as the median duration of therapy (mDOT), median duration of response (mDOR) and median time to progression (mTTP) were less frequently reported than mOS and mPFS (Supplementary Table 13).

### Tumor response

Tumor response for each arm was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) or RECIST 1.1 criteria for all but four trials [30,33,73,79]. Less than half the trials also assessed tumor response using modified RECIST (mRECIST) or immune-related RECIST (irRECIST); therefore RECIST results are shown. In the 1L RCT setting, the objective response rate (ORR; i.e., complete response + partial response) median value was 12% (range: 1–26%) among active treatments and 1% (range: 0–1%) among placebo/BSC, while the disease control rate (DCR; i.e., complete response + partial response + stable disease) median value was 53% (range: 35–73%) among active treatment arms and 29% (range: 16–32%) among placebo/BSC arms (Supplementary Figure 9). In the 2L RCT setting, the ORR median value (range) was 7% (range: 4–18%) among active treatment



**Figure 4. Within-trial survival comparisons in first-line trials. (A) PFS. (B) Overall survival.** The error bars presented in Lee et al. (2020) [44] represent the 80% CI. 1L: First line; Atezo + beva, atezolizumab + bevacizumab; BSC: Best supportive care; cabozan; cabozantinib; HR: Hazard ratio; IO: Immuno-oncology agent; NA: Not applicable; NR: Not reported; NS: Not significant; OS: Overall survival; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; VEGFRI: Vascular endothelial growth factor receptor inhibitor.



**Figure 5. Grade ≥3, serious and discontinuation-related treatment-emergent adverse events in first-line trials.** 1L: First line; BSC: Best supportive care; IO: Immuno-oncology agent; NR: Not reported; RCT: Randomized controlled trial; TEAE: Treatment-emergent adverse event; TKI: Tyrosine kinase inhibitor; VEGFRI: Vascular endothelial growth factor.

arms and 1% (range: 0–4%) among placebo arms, and the DCR median value was 64% (range: 56–83%) among active treatment arms and 39% (range: 33–53%) among placebo arms (Supplementary Figure 10).

### Safety results

Treatment-emergent adverse events (TEAEs) were reported more frequently than treatment-related adverse events (TRAЕ). In the 1L setting, the median value (range) of patients experiencing grade ≥3, serious, and discontinuation-related TEAEs was 56 (range: 32–75%), 44 (range: 10–56%), and 13% (range: 0–41%) of patients, respectively (Figure 5). In the 2L setting, the median value of patients experiencing grade ≥3, serious, and discontinuation-related TEAEs was 65 (range: 19–79%), 40 (range: 26–50%), and 13% (range: 5–56%) of patients, respectively (Supplementary Figure 11).

### NMA feasibility

In addition to similar patient characteristics, the feasibility of performing an NMA relies on a network of treatments connected by common comparators assessed in RCTs and common outcomes reported within each network [16]. We examined the outcomes that could be indirectly compared through an NMA for all the treatments recommended by the NCCN Guidelines, based on the available RCT data and network structure (Supplementary Figure 12). Notably, FOLFOX could not be compared with other 1L treatments in an NMA because the in-trial comparator was doxorubicin [61]; since no other recommended treatments have been compared with doxorubicin in a trial setting, FOLFOX could not integrate into the treatment network. Similarly, nivolumab ± ipilimumab could not be compared with other 2L treatments in an NMA because its existing trials were single-arm studies.

Based on the currently available RCT data, key efficacy outcomes (i.e., OS, PFS, ORR and DCR) could be indirectly compared via NMA for the majority of recommended treatments in both 1L and 2L RCT settings. Less commonly reported efficacy outcomes such as TTP and DOT could also be indirectly compared via NMA for most treatments. DOR could be indirectly compared in 2L RCTs only. Serious and discontinuation-related TEAEs could be indirectly compared via NMA in both 1L and 2L settings, but grade  $\geq 3$  TEAEs could be indirectly compared in the 1L setting only.

### Discussion

The objective of this study was to determine the similarity of trials assessing recommended systemic treatments for advanced HCC. In general, we found that trials were largely similar based on design and inclusion criteria within respective 1L and 2L categories, aside from some older single-arm trials and placebo-controlled RCTs assessing sorafenib [30–32,35,37,38]. The design and patients' disease stage in 2L RCTs were also considered broadly similar and suitable for quantitative comparison.

Trials differed in some key patient characteristics. While age, sex, and prevalence of vascular invasion and extrahepatic spread were relatively similar across trials, the proportion of patients infected with hepatitis B and levels of AFP varied widely. Hepatitis B infection and AFP level may represent treatment effect modifiers and should be evaluated closely in any potential meta-analyses. For example, a review of over 11,000 patients with HCC in USA found that hepatitis B-related cases were associated with a significantly lower risk of mortality compared with cases related to alcohol, metabolic disorder and multiple etiologies [96]. Similarly, AFP is a biomarker often elevated in patients with HCC who are more likely to have viral etiology, cirrhosis, larger or multiple tumors and vascular invasion [97]. Ultimately, the best approach may be to perform quantitative studies using analyses of patient subgroups with underlying disease characteristics or comorbidities as reported by individual study authors to control for specific patient characteristics [13]. This method enables more nuanced information for healthcare decision makers to make targeted recommendations for patients based on the presence or absence of specific disease characteristics, such as bleeding risk, hepatitis B infection or AFP levels.

We also found generally robust reporting of key clinical efficacy outcomes, including mPFS, mOS and tumor response. There is broad consensus that mOS is the primary efficacy outcome of interest in determining a preferred treatment. Other efficacy outcomes, such as mPFS, mTTP and ORR, could be analyzed using NMA with relatively robust networks. However, there is some disagreement within the field on the usefulness of surrogate end points such as mTTP, mPFS and ORR [98–101], particularly for IO agents, which demonstrate different relationships between tumor response and disease progression than TKI and VEGFRI drugs [102,103]. In other words, although analyses of several efficacy outcomes may be possible in an NMA, the interpretation of analyses on surrogate end points must be performed with a deep understanding of the treatments involved and clinical implications of the findings. Indirect comparisons of serious TEAEs or TEAEs leading to discontinuation are also possible via NMA; however, we did not assess the practicality of indirectly comparing individual adverse events, and these analyses are typically less reliable due to heterogenous reporting and relative rarity.

### Limitations

The purpose of this study was to qualitatively review the literature; therefore, no quantitative comparisons can be drawn from this study. We noted the limited information or absence of reporting by trial authors on patient characteristics and outcomes of interest, particularly when the primary study involved a clinical trial registry entry or conference abstract with minimal information. For example, mRECIST criteria are considered to be more sensitive than RECIST criteria in assessing tumor response and predicting survival [104]; however, as noted in the Results, mRECIST criteria were used less frequently than RECIST and would therefore be more difficult to assess

for similarity in a quantitative analysis. Similarly, the reporting of TEAEs and TRAEs differed for specific safety events. We also did not assess the comparability of patient-reported outcomes, such as quality of life. However, we found that very few trials reported quality of life; therefore a robust assessment of similarity would not be possible.

There are several treatments being assessed as monotherapies or in novel combinations in patients with HCC [105,106]. This review is inherently limited by the rapidly evolving trial landscape in this field. However, our review demonstrates the need for treatments with improved efficacy and safety profiles, as we found that the typical overall survival for patients using recommended treatments in the RCT settings was approximately 12 months, and approximately one in seven patients discontinued trial participation (based on mOS median values of 13.4 months and 10.2 months in 1L and 2L settings, respectively, and median discontinuation due to TEAEs of 13%).

The relationship between performance status and survival (as well as other baseline disease characteristics) has been noted in both clinical trial and real-world studies [107,108]. The disease stage of patients enrolled in the clinical trials reviewed in this study appeared to be less severe (e.g., ECOG 0, Child–Pugh class A) than the majority of patients who typically present with advanced HCC [11]. Conversely, there is limited guidance available on the treatment of patients with more advanced disease (e.g., Child–Pugh class A) [109], since few interventional and observational studies have included patients with more severe disease [110–113]. Furthermore, most trials excluded patients based on other characteristics, such as bleeding risk and chronic infections; patients excluded for these reasons may experience worse outcomes with these treatments in real-world settings. Finally, treatments may be contraindicated or show worse safety profiles in patients with underlying comorbidities (e.g., hypertension) that were not explored here. In summary, efficacy and safety outcomes from individual trials and subsequent indirect comparisons may not be completely representative of the experience of HCC patients in the real world; treatment efficacy and safety should be considered in patients with more severe disease.

## Conclusion

Patients with advanced HCC who are eligible for systemic treatment exhibit a wide spectrum in physical function and disease severity, as well as other key patient characteristics. Our objective was to assess the similarity and outcomes reported by trials that measured the efficacy and safety of systemic HCC treatments recommended by the NCCN Guidelines. To our knowledge, this study is first similarity assessment of trials that include only treatments recommended by the NCCN Guidelines in both 1L and 2L settings. After examining trial inclusion criteria, patient characteristics, and reported outcomes, we determined that randomized trials assessing recommended treatments for HCC are largely similar and appropriate for indirect comparisons, and several efficacy and safety outcomes are possible to analyze in a quantitative manner. Special consideration should be applied in determining the appropriate outcomes for analyses, as well as potential subgroups based on demographic and clinical characteristics, that will be robust, clinically relevant, and enable decision-making in healthcare.

## Future perspective

There are several treatments under investigation for the treatment of advanced HCC, as well as trials assessing novel treatment combinations and/or sequencing of currently recommended treatments. These treatments, in combination with more widespread use of precision medicine approaches, have the potential to slow disease advancement and improve patient survival in the real world.

## Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/hep-2021-0003](http://www.futuremedicine.com/doi/suppl/10.2217/hep-2021-0003)

## Author contributions

A Aly, F Benavente and J-D Rueda contributed to study conception, design and revisions to the manuscript; S Ronnebaum and D Patel contributed to study design, data analysis, drafting and revision of the manuscript.

## Financial & competing interests disclosure

Funding for this study was provided by AstraZeneca. A Aly and F Benavente are former employees of AstraZeneca. J-D Rueda is an employee and stockholder of AstraZeneca. S Ronnebaum and D Patel are employees of OPEN Health. The authors have no other

relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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### Summary points

- Hepatocellular carcinoma (HCC) is often diagnosed in advanced disease stages, in which systemic treatments are the only recommended option.
- NCCN guidelines recommend several systemic treatments in the first-line (1L) and second-line (2L) settings for patients with advanced HCC.
- We performed a systematic literature review to identify all single arm and randomized trials assessing recommended treatments.
- After reviewing 5677 records, a total of 57 references (representing 50 trials) were included in the systematic literature review. Of these, 31 records (representing 24 trials) were further assessed for similarity within 1L and 2L groups.
- We found that trials in the 1L setting were largely similar, except that some of the early trials for sorafenib included patients with more severe disease, and that trials in the 2L setting were also generally similar.
- The median (range) of mOS values from RCTs in 1L patients was 13.4 (4.0–19.2) months (active treatments) and 4.2 (3.5–7.9) months (placebo), and the median (range) of mOS values from RCTs in 2L patients was 10.2 (8.5–13.9) months (active treatments) and 7.8 (7.3–10.6) months (placebo).
- Across all trials, the median (range) of patients experiencing grade  $\geq 3$ , serious, and discontinuation-related treatment-emergent adverse events was 57 (range: 19–79%), 43 (range: 10–56%) and 13% (range: 0–56%), respectively.
- Our review demonstrates the feasibility of quantitative comparisons of recommended treatments, as well as the survival, tumor response, and safety experienced by patients in 1L and 2L trial settings. Outcomes experienced by real-world patients may reflect more advanced disease stage, comorbidities and other factors.

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