Systematic Review
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An Efficacy and Safety Comparison of Regorafenib and Nivolumab in Unresectable Hepatocellular Cancer Patients: A Systematic Review

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Abstract

Objective. This systematic review aimed to compare the efficacy and safety of regorafenib and nivolumab, two FDA-approved second-line treatments for unresectable Hepatocellular Carcinoma (HCC). **Methods.** Literature comparing the efficacy and safety of regorafenib and nivolumab in unresectable HCC patients was systematically searched across seven databases, including: PubMed, SCOPUS, Cochrane Database of Systematic Reviews, ScienceDirect, EBSCOhost, EMBASE, and ProQuest, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The search was done on April 2nd, 2023. Study quality and risk of bias were assessed using the Agency for Healthcare Research and Quality (AHRQ) and ROBINS-1 tools. The selected studies were included in the qualitative data synthesis. **Results.** Three trials found that HCC patients taking nivolumab had statistically insignificantly longer OS, TTP, and progression-free survival than those on regorafenib. Nivolumab increased ORR, with largely partial responses, and mixed DCR, with little statistical significance. All three studies showed that nivolumab had fewer side effects and improved tolerance. **Discussion.** Three retrospective cohort studies with a total of 383 regorafenib-receiving cohorts and 230 nivolumab-receiving cohorts were included in the qualitative analysis. Nivolumab was found to be superior in regards of longer overall survival, longer time to progression, higher objective response rate, and lower adverse event occurrence. However, statistical significance was not achieved in most of the parameters. **Conclusions.** The use of nivolumab is preferable as the second-line systemic therapy for unresectable HCC. More high-quality studies are urgently needed to generate quantitative analysis, and to encourage the formation of guidelines for second-line systemic therapy.

Key Words: Unresectable Hepatocellular Carcinoma ▪ Regorafenib ▪ Nivolumab.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide, with an increasing incidence. In 2020, an estimated 905,700 people were diagnosed with, and 830,200 people died from liver cancer globally. The age-standardized incidence for new cases of and deaths from HCC were 9.5 and 8.7 per 100,000 people, respectively. Liver cancer was among the top three causes of cancer deaths, with the number of new cases and deaths expected to increase by 50% by 2040 (1-3). Early diagnosis and tumor staging are key for treatment and prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging system is often used to link tumor features, patient characterization, treatment options, and expected survival. HCC in BCLC class 0 (very early stage) or class A (early stage) is usually eligible for local ablation, resection, and liver transplantation. In BCLC class B (intermediate stage), transarterial chemoembolization (TACE) has become a standard for unresectable HCC. Patients with HCC BCLC class C (advanced stage), or class B who are

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not candidates for TACE, or have progressed after TACE are eligible for systemic therapy. For almost a decade, the treatment of advanced HCC was limited to sorafenib, an anti-angiogenic TKI. Later the first line treatment was updated to a combination of atezolizumab (a programmed death 1 (PD-1) inhibitor) and bevacizumab (an anti-Vascular Endothelial Growth Factor (VEGF)) which was proven to be superior in RCTs (4). Unfortunately, there is still uncertainty regarding the second-line treatments for patients who are still progressing after the first line treatment (5). Two examples of FDA-approved second line treatments are regorafenib (an oral multikinase inhibitor) and nivolumab (a PD-1 inhibitor) (6). Unlike existing reviews, which specifically focus on cases following sorafenib failure, this review takes a broader perspective to gather and compare the available literature regarding the efficacy and safety of these two second-line drugs for patients with unresectable HCC.

Methods

This study was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Literature related to the efficacy of nivolumab treatment in comparison with regorafenib treatment in patients diagnosed with unresectable hepatocellular carcinoma was systematically searched across seven databases, including: PubMed, SCOPUS, Cochrane Database of Systematic Reviews, ScienceDirect, EBSCOhost, EMBASE, and ProQuest. The general search terms used included: "unresectable hepatocellular carcinoma" OR "unresectable HCC", "Nivolumab", "Regorafenib", "Overall survival rate" OR "Progression free survival rate" OR "Adverse event" OR "Safety". The search was performed on April 2nd, 2023, with Table 1 showing the detailed keywords that were used for each database.

There was no limitation of the publishing period, but the language was limited to English. In consideration of the authors' proficiency in English, the decision was made to present this manuscript in English to ensure accurate and effective communication of the content. This choice allows for a comprehensive understanding and coherent presentation of the research findings. Manual searching through references was done to find additional studies. After duplicates were removed, the titles and abstracts were then screened. Potential literature underwent full-text review of suitable papers which were to be included in the data synthesis. Searching and screening were done independently by two investigators and the reasons for exclusion are given in the PRISMA flowchart (Figure 1).

Table 1. Keywords Used for Each Database

Database	Keywords
PubMed	((“Carcinoma, Hepatocellular/therapy”[Mesh]) AND (“Carcinoma, Hepatocellular/surgery”[Mesh])) AND “Nivolumab/therapeutic use”[Mesh] AND “regorafenib”[All Fields] OR regorafenib[Text Word] AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
Scopus	TITLE-ABS-KEY((unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety))
Cochrane Library	((“Carcinoma, Hepatocellular/therapy”[Mesh]) AND (“Carcinoma, Hepatocellular/surgery”[Mesh])) AND “Nivolumab/therapeutic use”[Mesh] AND “regorafenib”[All Fields] OR regorafenib[Text Word] AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
ScienceDirect	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
EBSCOhost	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
EMBASE	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
ProQuest	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)

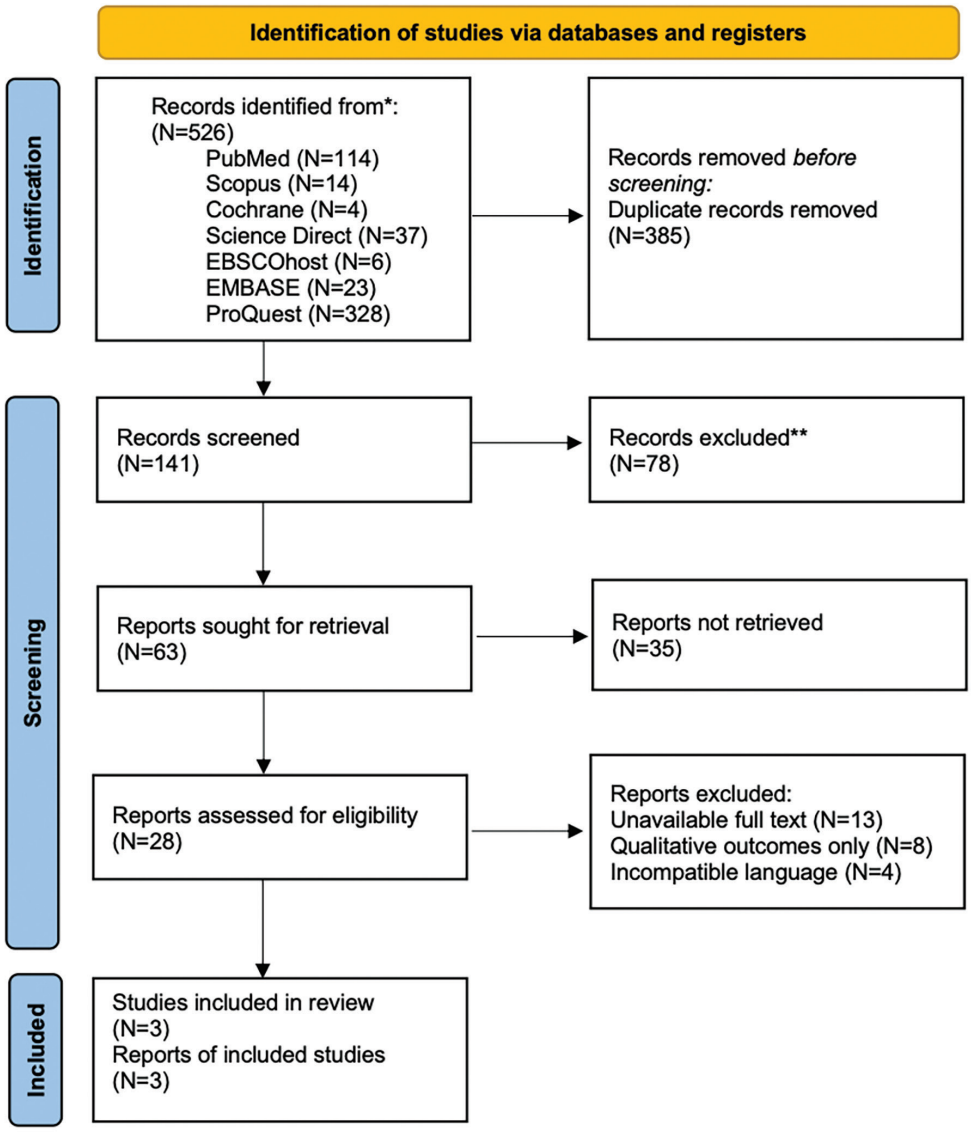

Figure 1. The PRISMA flow diagram of this study.

Study Eligibility Criteria

Inclusion criteria for studies to be included in the analysis were studies: 1) that had subjects diagnosed with unresectable hepatocellular carcinoma; 2) where the subjects were given Nivolumab medication; 3) there was a comparison with the intervention with Regorafenib treatment; and 4) that reported the efficacy of the treatment measured in terms of overall survival, progression-free survival, response rate, and adverse events. The criteria for studies to be excluded were: 1) literature reviews, cross-sectional studies, or case reports; 2) *in vitro* and animal studies; 3) Not using English; 4) Not reporting any quantitative results; 5) Single arm studies or those using a placebo as the comparator. The study designs included were Randomized Controlled Trials (RCT) and cohort studies, due to the high level of evidence in these study designs compared to other intervention study designs.

Data Extraction

The following data were extracted from each eligible study: 1) the authors and year of publication; 2) the study design; 3) the country in which the study was conducted; 4) the inclusion criteria; 5) the number of patients with treatment; 6) the mean age of the study populations; 7) the duration of follow up; 8) study outcomes, which included the parameters overall survival (OS) and/or progression free survival (PFS), time to progression (TTP), tumor response in the form of objective response rate (ORR) and disease control rate (DCR), and safety; 9) summary findings in the study. The data were extracted by two authors independently.

Quality Assessment and Data Synthesis

Quality assessment of the included studies was done using the Agency for Healthcare Research and Quality (AHRQ) tools. Risk of bias was also undertaken comprehensively with the ROBINS-1 tool for non-randomized studies if the studies included were not randomized. A study was considered good if it received 3 or 4 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome domain. A study was considered fair if it received 2 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome domain. A study was considered poor if it received 0 or 1 star in the selection domain AND 0 stars in the comparability domain AND 0 or 1 star in the outcome domain (7). Extracted data were summarized in tables and narrative synthesis was performed to describe the data. Due to the heterogeneity of the included articles with regard to outcomes of interest to our review, we are unable to analyze and synthesize the data quantitatively. We analysed and reported (qualitative) data in accordance with our study objectives regarding the safety and efficacy of the intervention, which included overall survival, progression-free survival, response rate, and safety in terms of adverse events.

Results

Study Selection

The literature search across seven databases resulted in 526 hits. After removal of 385 duplicates, 141 titles and abstracts were screened to exclude 78 irrelevant papers. Out of the remaining 63 papers, only 28 papers underwent full-text review. There were only three studies that fully met the inclusion criteria, and were hence included in the qualitative data synthesis. The summary of study selection is presented in the PRISMA flow diagram (Figure 1). The list of excluded studies at the full-text level is available in Supplementary File 1.

Study Characteristics and Risk of Bias

All three included studies were retrospective cohort in design, with a total of 383 cohorts who received regorafenib and 230 cohorts who received nivolumab as their second line systemic HCC therapy (8-10). Two of them were from South Korea (conducted in 2020), and one from Taiwan (conducted in 2021). The study by Lee et al. included adult patients with HCC confirmed radiologically or histologically who had received regorafenib or nivolumab. They included 102 patients in the regorafenib group (with a mean age of 62 years old) and 48 patients in the nivolumab groups (with a mean age of 61 years old). Their follow up duration was 1 year and 6 months. The research was supported by the Seoul National University Hospital Research Fund. The study by Choi et al. also included patients with confirmed HCC receiving regorafenib or nivolumab after sorafenib failure, who had Barcelona Clinic Liver Cancer (BCLC) stage B or C, and at least one measurable target lesion based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST). They included 223 patients in the regorafenib group (with a mean age of 58.5 years old) and 150 patients in the nivolumab groups (with a mean age of 56.9 years old). Their follow up duration was six months. The funding was not clearly reported. Lastly, the study by Kuo et al. included patients with unresectable HCC

receiving regorafenib or nivolumab after sorafenib failure, who had Child-Pugh class A or B. They included 58 patients in the regorafenib group (with a mean age of 63.4 years old) and 32 patients in the nivolumab groups (with a mean age of 62 years old). Their follow up duration was one year. Although the funding was not clearly stated, the authors declared that the research was conducted without any commercial or financial relationships that could be taken as a potential conflict of interest. The study characteristics are available in Table 2. Using the AHRQ tools and its standards, all three included studies were assessed to be of good quality. The detailed assessment aspects are available in Table 3. The risk of bias was assessed using ROBINS-I tools, as detailed in Table 4.

Table 2. The Characteristics of Included Studies

Author; year of publication	Study design	Country	Inclusion criteria	Number of patients with treatment		Regorafenib	Nivolumab	Follow up duration
				Regorafenib (dose)	Nivolumab (dose)	Mean age (In years (SD)		
Lee et al., (6) 2020	Retrospective cohort	South Korea	Adult patients (>18 years old), had received regorafenib or nivolumab treatment, confirmed HCC radiologically or histologically.	102 (160 mg once/day for 21 days of each 28 days cycle; adjusted by the amount of 40 mg or transient interruption)	48 (3mg/kg every two weeks)	62 (56-71)	61 (54-67)	1 year and 6 months
Choi et al., (7) 2020	Retrospective cohort	South Korea	Patients that had been diagnosed with HCC based on pathological confirmation and computed imaging, received regorafenib or nivolumab after sorafenib failure, had a BCLC stage B or C, and had at least 1 measurable target lesion based on mRECIST.	223 (160 mg once/day for the first 3 of 4 weeks cycle)	150 (3 mg/kg every two weeks)	N/A	N/A	Minimum of 6 months
Kuo et al., (8) 2021	Retrospective cohort	Taiwan	Patients that had an unresectable HCC (intermediate or advanced stage), received regorafenib or nivolumab after sorafenib failure, and had Child-Pugh class A or B.	58 (160 mg once/day for the first 3 of 4 weeks cycle)	32 (3 mg/kg every two weeks)	N/A	N/A	1 year

SD=Standard Deviation; HCC±Hepatocellular carcinoma; BCLC±Barcelona Clinic Liver Cancer; mRECIST±modified Response Evaluation Criteria in Solid Tumours.

Table 3. Quality Assessment of Included Studies Using the AHRQ Tools

Study	Selection				Comparability	Outcome			Total quality score	AHRQ Standard
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Design or analysis controlled for confounders	Assessment of outcome	Follow-up length	Loss to follow-up rate		
Lee et al., 2020	a (*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	8	Good
Choi et al., 2020	a(*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	8	Good
Kuo et al., 2021	a(*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	8	Good

(*) Stars are given for each of the study aspects.

Table 4. Risk of Bias Assessment of Included Studies Using the ROBINS-I Tools

Study	Pre-intervention			At intervention	Post-intervention				Overall risk of bias
	Representativeness of exposed cohort	Bias due to confounding	Bias in selection of participant into the study	Bias in classification of interven-tions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement outcome	Bias in selection of the reported result	Low/moderate/serious/critical
Lee et al., 2020	low	low	low	low	low	low	low	low	low
Choi et al., 2020	low	low	low	low	low	low	low	low	low
Kuo et al., 2021	low	moderate	low	low	low	low	moderate	low	low

Study Outcomes

All three included studies reported the overall survival, time to progression, tumor response, and safety profile. All three studies showed that HCC patients receiving nivolumab had statistically insignificant longer OS when compared with regorafenib. Lee et al. found statistically significant improvement in OS with nivolumab after multivariate analysis (8). Choi et al. added that there was no significant difference in the PFS (9). Both the studies by Lee et al. and Kuo et al. showed that nivolumab-receiving patients had statistically insignificantly longer TTP than regorafenib-receiving patients (8, 10). In contrast, cohorts receiving regorafenib in the study by Choi et al. showed longer median TTP compared to those receiving nivolumab (although the difference was not statistically significant) (9).

All three studies reported that nivolumab administration in unresectable HCC cases resulted in higher ORR than regorafenib (statistical significance was achieved in two studies). Unfortunately, almost all of them were partial responses and the rate of complete response was very low. Contradicting results were shown in the DCR, as Lee et al. and Kuo et al. both showed that nivolumab resulted in a higher DCR when compared with regorafenib (8, 10). On the other hand, Choi et al. showed that regorafenib resulted in a higher DCR (9). It is important to note that no statistical significance was found in the three included studies. In regards of safety, the superiority of nivolumab over regorafenib was shown in all three studies with lower adverse effect occurrence and better tolerance. The detailed results of the included studies are presented in Table 5, along with the summary findings of each study.

Discussion

The three studies examined overall survival, progression times, tumor responses, and safety profiles in HCC patients treated with nivolumab and regorafenib (Tables 2, 3, and 5). While all the studies showed a trend towards longer overall survival with nivolumab, statistical significance was only found in Lee et al.'s multivariate analysis (8). Time to progression favored nivolumab in two studies, but Choi et al. reported longer times with regorafenib (9). Nivolumab led to higher objective response rates, mainly partial responses, with two studies showing statistical significance. Disease control rates varied across studies, without statistical significance. Overall, nivolumab demonstrated better safety profiles compared to regorafenib in all three studies.

Sorafenib was the only approved systemic treatment of choice for unresectable HCC after the SHARP phase III trial in 2008, which showed a significant, 30% improvement in the OS compared to the placebo group (10.7 vs. 7.9 months) (11). The first line systemic treatment regimen was updated to atezolizumab and bevacizumab after the IMBRACE-150 phase III trial in 2020, which showed 34% improvement in OS and PFS when

Table 5. Outcomes of the Included Studies

Author, year of publication	Study Outcomes				Summary Findings
	Overall Survival and Progression Free Survival	Time to Progression	Tumor Response	Safety	
Lee et al., 2020	Median OS In months (95%CI) Regorafenib: 6.9 (3.5-13.1) Nivolumab: 5.9 (3.2-18.1) P=0.77 by log-rank test Multivariate analysis aHR: 0.54; 95%CI 0.30-0.96 P=0.04 in favor to nivolumab	Median TTP In months (95%CI) Regorafenib: 3.3 (2.0-5.3) Nivolumab: 4.0 (1.8-8.7) P=0.40 by log-rank test Multivariate analysis aHR: 0.81; 95%CI 0.51-1.30 P=0.48 in favour to nivolumab	No patient achieved a complete response Partial response by mRECIST (ORR) Regorafenib: 6/102 (5.9%) Nivolumab: 8/48 (16.7%) P=0.041 in favour to nivolumab DCR Regorafenib: 47.1% Nivolumab: 50.0% P=0.58	Adverse events occurrence Regorafenib: 24/102 (23.5%) Nivolumab: 8/48 (16.7%) P=0.34 Major cause of drug discontinuation: hepatic decompensation (8.3% in nivolumab group and 9.8% in regorafenib group)	Nivolumab was associated with statistically insignificantly longer OS, longer TTP, higher disease control rate, and lower adverse events. Nivolumab showed statistically significantly objective response rate
Choi et al., 2020	Median OS In weeks (95%CI) Regorafenib: 30.9 (28.9-35.6) Nivolumab: 32.6 (21.7-42.9) HR (95%CI) = 0.83 (0.64-1.07) in favour to nivolumab P=0.154 Median PFS In weeks (95%CI) Regorafenib: 12.0 (9.1-13.3) Nivolumab: 7.1 (6.3-10.1) HR (95%CI) = 0.85 (0.69-1.06) in favour to nivolumab P=0.150	Median TTP In weeks (95%CI) Regorafenib: 12.1 (10.6-14.6) Nivolumab: 7.9 (7.0-15.3) HR (95%CI) = 0.95 (0.77-1.19) in favour to nivolumab P=0.680	Only 1/150 (0.7%) of the nivolumab cohort achieved complete response, 19/150 had partial response ORR Regorafenib: 9/223 (4.0%) Nivolumab: 20/150 (13.3%) P=0.002 DCR Regorafenib: 66/223 (48.5%) Nivolumab: 55/150 (40.4%) P=0.222	Rate of dose reductions due to intolerance Regorafenib: 75/223 (33.6%) Nivolumab: 5/150 (3.3%) Rate of toxicity-related discontinuation Regorafenib: 15/223 (6.7%) Nivolumab: 3/150 (2.0%)	Nivolumab was associated with statistically insignificantly longer OS and longer PFS. Although it showed statistically significantly higher ORR and better safety profile
Kuo et al., 2021	Number of deaths Regorafenib: 28 (48.3%) Nivolumab: 17 (53.1%) Median OS In months Regorafenib: 17.3 Nivolumab: 21.9 P=0.966	Median TTP In months Regorafenib: 2.6 Nivolumab: 3 P=0.786	There were 2 (4.3%) had complete response in the regorafenib group ORR Regorafenib: 6.4% Nivolumab: 16% P=0.190 DCR Regorafenib: 31.9% Nivolumab: 44% P=0.309	TRAE Regorafenib: occurred in 68% of patients (the most common is hand-to-food skin reaction in 23.8%) Nivolumab: occurred in 37.5% of patients (the most common is fatigue in 12.1%) P=0.006	Nivolumab had statistically insignificantly longer OS, longer TTP, higher ORR and DCR. It showed statistically significantly lower rate of TRAE.

OS=Overall survival; PFS=Progression free survival; ORR=Objective response rate; DCR=Disease control rate; TRAE=Treatment-related adverse events; CI=Confidence interval; TTP=Time to progression; aHR=Adjusted hazard ratio; mRECIST=modified Response Evaluation Criteria in Solid Tumors.

compared to sorafenib (19.2 vs. 13.4 months) (4). However, there were several other phase III trials conducted, the results of which provided second line treatment options for unresectable HCC. The RESORCE phase III trial in 2017 reported that regorafenib (a multikinase inhibitor) showed a significant, 27% longer OS than the placebo in patients progressing after sorafenib (10.6 vs 7.8 months) (12). Other agents, such as cabozantinib (Celestial phase III trial), ramucirumab (REACH-2 phase III trial), apatinib (ALHEP phase III trial), and pembrolizumab (KEYNOTE-394),

Table 6. AMSTAR-2 Tool for Systematic Review

Domain number	Critical or non-critical	Content of the domain	Yes or partial yes (%)	No (%)
1	Non-critical domain	Did the research questions and inclusion criteria for the review include the components of PICO[a]?	100	0
2	Critical domain	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	0	100
3	Non-critical domain	Did the review authors explain their selection of the study designs for inclusion in the review?	100	0
4	Critical domain	Did the review authors use a comprehensive literature search strategy?	50	50
5	Non-critical domain	Did the review authors perform study selection in duplicate?	100	0
6	Non-critical domain	Did the review authors perform data extraction in duplicate?	100	0
7	Critical domain	Did the review authors provide a list of excluded studies and justify the exclusions?	100	0
8	Non-critical domain	Did the review authors describe the included studies in adequate detail?	100	0
9	Critical domain	Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	100	0
10	Non-critical domain	Did the review authors report on the sources of funding for the studies included in the review?	100	0
11	Critical domain	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	N/A
12	Non-critical domain	If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	N/A
13	Critical domain	Did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review?	100	0
14	Non-critical domain	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	N/A
15	Critical domain	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A	N/A
16	Non-critical domain	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	100	0

also showed superiority in prolonging the overall survival when compared to the placebo (13-16). However, only three regimens (i.e., regorafenib, cabozantinib, and ramucirumab) were approved for the advanced HCC after progression on sorafenib (6).

Three additional second line systemic therapy options were approved on the basis of promising phase Ib/II studies, including nivolumab, pembrolizumab, and ipilimumab (in combination with nivolumab). The CheckMate 040 phase II trial assessed nivolumab as a monotherapy, and demonstrated an ORR of 14% with a median duration of response of 17 months, overall survival was 15.6 months, and the treatment was well tolerated (17). In the CheckMate 459 phase III trial, nivolumab was compared with sorafenib in the first line setting, and a median OS of 16.4 months was reported for nivolumab and 14.7 months for sorafenib (P=0.07) (18).

The improved OS in the nivolumab group compared to the regorafenib group might be explained by the tumor response to the therapy. Targeted therapies, including multikinase inhibitors, have lower response rates and higher therapeutic resistance in HCC as the driver oncogenes have not yet been accurately identified. Hence, most responses are short lived due to the emergence of therapeutic resistance. However, treatment with immune checkpoint inhibitors (such as nivolumab) results in more durable tumor responses, although often in a lower percentage of patients (19). Other studies showed that previous first line systemic treatment might also influence the OS of the second line systemic therapy. Zhai et al. showed that patients receiving regorafenib after receiving lenvatinib showed longer OS compared to those receiving sorafenib as the first line therapy (15.9 vs 11.7 months, P=0.045) (20).

Literature that studied the safety profile of regorafenib in other types of cancer (i.e., metastatic colorectal cancer) also reported similar TEAEs in HCC cases. One study reported that TEAE occurred in 96% of patients, which led to dose reduction in 30% of patients, and treatment discontinuation in 17% of patients (21). Nivolumab monotherapy showed more tolerable adverse effects even when used in other cancer types (i.e., malignant melanoma) with 71% any-grade treatment-related adverse effects and only 10% grade 3 to 4 treatment related adverse events (22). Therefore, the findings in this study are consistent with previous studies regarding the safety and tolerability of the therapy.

The results presented might differ from previous studies due to the differences in patient baseline characteristics. For example, the ORR and DCR observed in the study by Choi et al. were lower when compared with previous phase II trials as previous trials only included patients with Child-Pugh class A and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (9). Therefore, it is important to include the patients' baseline characteristics as well as the treatment regimens (i.e., dosing and duration of treatment) in consideration before interpreting the results of these studies.

Limitations of the Study

This study only includes three studies with a number of cohorts too small to produce a comprehensive comparison between the treatment groups. The three studies included are all retrospective cohorts, as no RCT was found during the literature search. Future studies should include more literature, especially future RCTs, that compare second line systemic treatment options to the first lines or to other second lines. Quantitative analysis should be conducted if adequate literature is available with low heterogeneity, to provide statistical analysis of this comparison. A longer duration of follow up would be ideal to provide more data regarding the OS, TTP, and safety profile of the therapy.

Conclusions

A total of three retrospective cohort studies was found comparing the efficacy and safety of regorafenib and nivolumab as the second-line systemic treatment for unresectable advanced-stage HCC. Nivolumab was shown to generally have longer OS, longer PFS, longer TTP, better ORR, better DCR, and lower adverse events compared to regorafenib. Statistical significance was only achieved in some parameters in each included study. Therefore, the use of nivolumab is preferable as the second line systemic therapy for unresectable HCC. Nevertheless, the patients' baseline characteristics, dosing regimen, and prior therapy should be taken into consideration and may alter the prognosis of the patients. More high-quality studies are urgently needed to generate quantitative analysis and to encourage the formation of guidelines for second line systemic therapy of advanced stage HCC.

What Is Already Known on This Topic:

Atezolizumab (a programmed death 1 (PD-1) inhibitor) and bevacizumab (an anti-Vascular Endothelial Growth Factor (VEGF)) are the first-line treatment of advance and unresectable HCC. For patients who continue to experience disease progression after initial treatment, second line treatment is prescribed. Among the FDA-approved second-line options are regorafenib (an oral multikinase inhibitor) and nivolumab (a PD-1 inhibitor).

What This Study Adds:

In terms of key efficacy and safety outcomes, nivolumab demonstrated superior performance when compared to regorafenib in the treatment of unresectable advanced stage HCC. Nivolumab gave longer overall survival, longer progression free survival, longer time to progression, better objective response rate, better disease control rate, and a lower incidence of adverse events. On the basis of these findings, nivolumab emerges as the preferred choice for second-line systemic therapy in patients with unresectable HCC.

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Supplementary 1. List of Excluded Studies on the Level of Full Text Assessment

Authors; year	Title	Reasons for exclusion
Grothey et al., 2013	Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial	Unavailable full text
Bruix et al., 2017	Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial	Unavailable full text
Demetri et al., 2013	Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial	Qualitative outcomes
Kim et al., 2023	Regorafenib plus nivolumab in unresectable hepatocellular carcinoma: the phase 2 RENOBATE trial	Unavailable full text
Duffaud et al., 2019	Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study	Unavailable full text
Lei et al., 2022	Efficacy and safety of monotherapy and combination therapy of immune checkpoint inhibitors as first-line treatment for unresectable hepatocellular carcinoma: a systematic review, meta-analysis and network meta-analysis	Unavailable full text
Liu et al., 2021	First-Line Systemic Treatment Strategies for Unresectable Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials	Unavailable full text
Hsu et al., 2020	Predictors of response and survival in patients with unresectable hepatocellular carcinoma treated with nivolumab: real-world experience	Qualitative outcomes
Jacome et al., 2021	Efficacy and safety associated with immune checkpoint inhibitors in unresectable hepatocellular carcinoma: A meta-analysis	Unavailable full text
Armengol et al., 2018	Hepatocellular carcinoma: Present and future	Incompatible language

Authors; year	Title	Reasons for exclusion
Yoo et al., 2020	Regorafenib in previously treated advanced hepatocellular carcinoma: impact of prior immunotherapy and adverse events	Unavailable full text
Sung et al., 2020	Real-world outcomes of nivolumab in patients with unresectable hepatocellular carcinoma in an endemic area of hepatitis B virus infectio	Qualitative outcomes
Zaniboni et al., 2015	Regorafenib in patients with metastatic colorectal cancer: a review and an update	Incompatible language
Yang et al., 2023	Regorafenib compared to nivolumab after sorafenib failure in patients with hepatocellular carcinoma: A systematic review and meta-analysis	Unavailable full text
Schultheiss et al., 2018	Hepatocellular Carcinoma: New multimodal therapy concepts	Incompatible language
Lee et al., 2022	Determinants of Survival and Post-Progression Outcomes by Sorafenib–Regorafenib Sequencing for Unresectable Hepatocellular Carcinoma	Qualitative outcomes
Vogel et al., 2021	Advances in systemic therapy for the first-line treatment of unresectable HCC	Unavailable full text
Kim et al., 2023	Sorafenib versus nivolumab after lenvatinib treatment failure in patients with advanced hepatocellular carcinoma	Unavailable full text
Kudo et al., 2019	Targeted and immune therapies for hepatocellular carcinoma: predictions for 2019 and beyond	Qualitative outcomes
Parisod et al., 2017	Treatment of advanced hepatocellular carcinoma : Novel agents and role of local therapy	Incompatible language
Fulgenzi et al., 2022	Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: A network metanalysis of phase III trials	Unavailable full text
Xie et al., 2021	Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world	Qualitative outcomes
Hsu et al., 2022	Regorafenib for Taiwanese patients with unresectable hepatocellular carcinoma after sorafenib failure: Impact of alpha-fetoprotein levels	Qualitative outcomes
Personeni et al., 2018	Regorafenib in hepatocellular carcinoma: latest evidence and clinical implications	Qualitative outcomes
Huang et al., 2022	Regorafenib Combined with PD-1 Blockade Immunotherapy versus Regorafenib as Second-Line Treatment for Advanced Hepatocellular Carcinoma: A Multicenter Retrospective Study	Unavailable full text

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