Tzu Chi Medical Journal 2024; 36 (3): 340-348

Original Article

Efficacy of PD-1/PD-L1 inhibitors in advanced hepatocellular carcinoma: A systematic review and meta-analysis

*Tzu-Rong Peng, Li-Jou Yang, Ta-Wei Wu**

Department of Pharmacy, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan

Submission : 27-Jun-2023
Revision : 04-Sep-2023
Acceptance : 22-Sep-2023
Web Publication : 07-Nov-2023

Abstract

Objectives: This study aimed to investigate the efficacy and safety of programmed cell death-1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors in patients with advanced hepatocellular carcinoma (HCC). **Materials and Methods:** PubMed, EMBASE, and the Cochrane Library were searched for articles published until November 2022. Studies reporting the efficacy of PD-1/PD-L1 inhibitors in patients with advanced HCC were eligible for inclusion. The outcomes were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and ≥ Grade 3 treatment-related adverse events (TrAEs). **Results:** Fourteen trials with 4515 patients with HCC were included. Our results showed that treatment with PD-1/PD-L1 inhibitors was associated with better ORR and DCR than that with control (placebo or sorafenib or lenvatinib) (odds ratio [OR], 3.89; 95% confidence interval (CI), 2.55–5.95 and OR, 1.47; 95% CI, 1.11–1.95, respectively). The overall hazard ratio (HR) of PFS and OS were 0.66 (95% CI 0.56–0.78) and 0.65 (95% CI 0.55–0.77), respectively. In subgroup analysis, PD-1/PD-L1 inhibitor combination therapy had an advantage in terms of PFS (HR: 0.57 vs. 0.81) compared to that of PD-1/PD-L1 monotherapy. The incidence of grade 3–5 TrAEs was not significantly higher with PD-1/PD-L1 inhibitors than that with the control (OR, 1.12; 95% CI, 0.70–1.81). However, the combination of PD-1inhibitor with higher incidence of Grade 3–5 TrAEs (OR: 2.04, 95% CI 0.66–6.32) than the combination PD-L1 inhibitor (OR: 0.95, 95% CI 0.50–1.81). **Conclusion:** The combination of PD-1/PD-L1 inhibitors and targeted agents significantly improved the clinical outcomes in patients with advanced HCC. However, the incidence of Grade 3–5 TrAEs with PD-1 inhibitor combination therapy was higher than the combination PD-L1 inhibitor.

Keywords: *Hepatocellular carcinoma, Meta-analysis, Programmed cell death-1, Programmed death ligand 1*

Introduction

Hepatocellular carcinoma (HCC) is one of the malignant tumors with the highest mortality rate and the fourth-leading cause of cancer-related death worldwide [1]. Systemic therapy is standard treatment for unresectable or metastatic HCC. Sorafenib is the first targeted therapy drug approved by the US Food and Drug Administration and is the first-line treatment drug for HCC. Lenvatinib was approved in 2017 as the first-line treatment for HCC after sorafenib; however, its efficacy remains unsatisfactory [2,3].

Immunotherapy has achieved significant clinical success in cancer treatment. To date, many clinical trials have shown that the survival rate of patients with advanced cancer can be improved by treatment with immune checkpoint inhibitors (ICIs) [4-6].

Among ICIs, anti-programmed cell death 1 (anti-PD-1)/programmed cell death ligand 1 (PD-L1) are novel and promising therapies that have been effective in prolonging survival in patients with advanced HCC [7,8]; however, they have not replaced the traditional first-line treatment drugs sorafenib or lenvatinib. In addition, several single-arm clinical trials have reported the efficacy of PD-1/PD-L1 inhibitors in advanced HCC [9-11]. These clinical trials differed in their clinical stage, sample sizes, and response assessment criteria. Furthermore, the efficacy of single-drug therapy for HCC is

Address for correspondence: Dr. Ta-Wei Wu, Department of Pharmacy, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 289, Jianguo Road, Xindian, New Taipei, Taiwan.
E-mail: taiwei@tzuchi.com.tw

How to cite this article: Peng TR, Yang LJ, Wu TW. Efficacy of PD-1/PD-L1 inhibitors in advanced hepatocellular carcinoma: A systematic review and meta-analysis. Tzu Chi Med J 2024;36(3):340-8.

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_159_23

limited, and the possible combination of different ICIs and ICIs with targeted agents has been investigated in many clinical trials [12].

Recently, many randomized controlled trials (RCTs) [7,8,13-15] and observational studies [16-18] have been reported. Therefore, we performed an updated meta-analysis to elucidate the effects of PD-1/PD-L1 inhibitors in patients with advanced HCC.

Materials and methods

Research strategy and study selection

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. The present study was prospectively registered in the PROSPERO registry (registration number: CRD42023387214).

We included RCTs and observational studies (either cohort or case–control) that evaluated the effects of PD-1/PD-L1 inhibitors in patients with advanced HCC. These included PD-1 inhibitors (nivolumab, pembrolizumab, camrelizumab, cemiplimab, penpulimab, tislelizumab, toripalimab, and sintilimab) and PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab). We searched the PubMed, Cochrane Library, and EMBASE databases, limiting the search to human patients published until November 30, 2022. The search strategy is presented in Box 1. All retrieved articles were reviewed. Two reviewers (L. J. Y. and T. R. P.) independently screened all titles and abstracts and evaluated relevant articles. T. W. W serves as the final reviewer when L. J. Y. and T. R. P. disagree.

Inclusion and exclusion criteria

We adopted the following inclusion criteria: (1) study type of literature was a prospective clinical trial or real-world study; (2) PD-1/PD-L1 inhibitor monotherapy or combination with other therapy as intervention treatments; (3) enrolled patients with advanced HCC; and (4) the collected data were sufficient to evaluate treatment efficacy including overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (TrAEs). Studies with any of the following features were excluded: (1) single-arm study, (2) no related data, and (3) monotherapy with cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors.

Data extraction

Data were independently extracted, analyzed, and recorded on a predeveloped data extraction sheet by two reviewers (L. J. Y. and T. R. P.). The final decision was reached after consultation with a third reviewer and a team consensus. We extracted the first author, published year, study registration number, study design, treatment regimen, number of patients, measured outcomes (ORR, DCR, OS, and PFS), and TrAEs from the studies. The hazard ratios (HRs) of the time-to-event variables (OS and PFS) were directly extracted from the original studies or estimated indirectly using the reported number of events and the corresponding *P* values for the log-rank statistics.

Quality of included studies

Two authors (T. W. W. and L. J. Y.) separately assessed the quality of the included studies. For RCTs, bias was categorized as low, unclear, or high (green, yellow, or red) in each study, using the revised risk-of-bias 2.0 method (version 2.0). We determined the risk of bias for domain allocation concealment, randomization, blinding, incomplete outcome data, selective outcome reporting, and other biases. We used the Newcastle–Ottawa scale to assess the quality of observational studies [20]. The total score of this scale is 9 points. High-quality research results are rated ≥6 points. This scale evaluates quality based on the following three domains: Reporting of participant selection, comparability, and outcome assessment.

Statistical analyses

We calculated the pooled odds ratio (OR) and 95% confidence interval (CI) for ORR, DCR, and TrAEs, as well as the pooled HRs and 95% CI for OS and PFS. The pooled ORs and HRs were calculated using the DerSimonian and Laird random-effects meta-analysis [21] under the assumption of significant heterogeneity. Heterogeneity among studies was quantified using the I^2 test, and I^2 >50% was considered substantial heterogeneity. $P < 0.10$ was considered statistically significant. We constructed a funnel plot and performed Egger's and Begg's tests to assess publication bias. The Egger's and Begg's tests results showed no publication bias with a $P > 0.05$. Statistical analyses were performed according to the Cochrane Handbook for the Statistical Review of Interventions (version 6.2) [3]. This study used Review Manager Software (RevMan) (version 5.4; Oxford, UK) and Comprehensive Meta-analysis (CMA) software for statistical analysis.

Results

Selection of study

We identified 614 records from the PubMed, EMBASE, and Cochrane electronic databases. Forty-seven studies were removed because of duplication, and 130 studies were excluded because they were not the targets of this study. After excluding these studies, we reviewed 437 studies based on the titles and abstracts, and 423 studies were excluded because of irrelevant titles or content records. Fourteen studies met our inclusion criteria. The Systematic Reviews and Meta-Analyses (PRISMA) flowchart shows the detailed process of study selection [Figure 1].

Characteristics of eligible studies

Fourteen studies with 4515 patients were included in this meta-analysis. Of these studies, six were RCTs and eight were retrospective studies. All the studies were published between 2020 and 2022. The characteristics of the included studies are presented in Table 1. The results of the quality assessment of the seven RCTs are shown in Figure 2. Four RCTs [7,8,13,15] were discovered to have low risk in all the domains of assessment; only two studies [14,17] had a high risk of selection bias (allocation concealment) and performance bias (blinding of participants and personnel). However, the results of the quality assessment of the eight cohort studies

Box 1: PUBMED on November 30, 2022

MeSH terms

1. "immune checkpoint inhibitor" = 7270
2. "hepatocellular carcinoma" = 100,821.

Text terms

1. "programmed death-ligand 1" = 15,332
2. "nivolumab" = 8804
3. "pembrolizumab" = 8020
4. "atezolizumab" = 2586
5. "durvalumab" = 1290
6. "avelumab" = 837
7. "camrelizumab" = 357
8. "cemiplimab" = 289
9. "tislelizumab" = 126
10. "toripalimab" = 162
11. "sintilimab" = 300
12. "penpulimab" = 9
13. "hepatocellular carcinoma" = 141,136.

Search strings:

[(1 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14) =34,088 AND (2 OR 15) =141,136] = 1438.

AND (randomized controlled trial or retrospective study) =207.

Cochrane Library on November 30, 2022.

MeSH terms

1. "immune checkpoint inhibitor" = 91
2. "hepatocellular carcinoma" = 2040.

Text terms

3. "programmed death-ligand 1" = 777
4. "nivolumab" = 2591
5. "pembrolizumab" = 2583
6. "atezolizumab" = 1234
7. "durvalumab" = 943
8. "avelumab" = 348
9. "camrelizumab" = 169
10. "cemiplimab" = 85
11. "tislelizumab" = 152
12. "toripalimab" = 102
13. "sintilimab" = 129
14. "penpulimab" = 11
15. "hepatocellular carcinoma" = 5753.

Search strings:

[(1 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14) =7,741 AND (2 OR 15) = 5753] =374.

EMBASE on November 30, 2022.

Emtree term

1. "immune checkpoint inhibitor" = 17,270
2. "hepatocellular carcinoma" = 187,651.

Search strings:

3. (1 AND 2) = 1162
4. AND "human"/de=1111
5. AND (randomized controlled trial OR observational study OR retrospective study) = 33.

showed that assessment scores ranged from 6 to 8. All eight studies were adjusted for at least one other potentially crucial confounder. None of the studies described the adequacy of the follow-up of the cohorts.

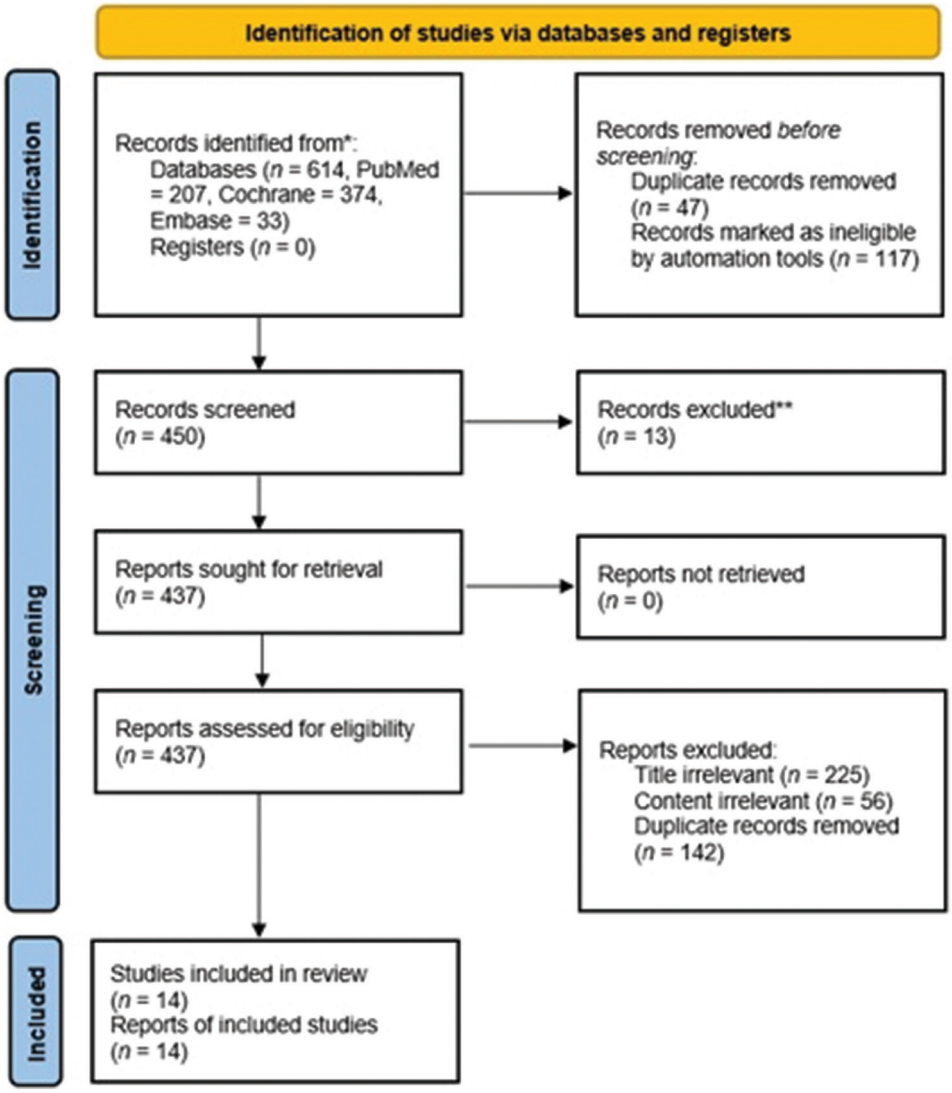

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection. *If feasible to do so, report the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools

Effects on ORR and disease control rate

Twelve studies provided ORR and DCR outcomes. Treatment with PD-1/PD-L1 inhibitors was associated with better ORR than that with standard care (placebo or sorafenib or lenvatinib) [OR, 3.89; 95% CI, 2.55–5.95; I^2 = 72%; P < 0.001, Figure 3a]. The PD-1/PD-L1 inhibitors had better DCR than the controls [OR, 1.47; 95%CI, 1.11–1.95; I^2 = 68%; P = 0.008, Figure 3b].

Effects on progression-free survival and overall survival

Ten studies examined the PFS and OS results. Treatment with PD-1/PD-L1 inhibitors was associated with greater improvement in PFS than that with standard care [HR, 0.66; 95% CI, 0.56–0.78; P < 0.0001, Figure 4a]. Analysis of PFS showed significant heterogeneity among the studies (I^2 = 69%). Compared with controls (sorafenib in first line or placebo in second line), treatment with PD-1/PD-L1 inhibitors was associated with significantly improved OS [HR, 0.65; 95% CI, 0.55–0.77; I^2 = 64%; P < 0.0001, Figure 4b].

Treatment-related adverse events

Eleven studies analyzed the TrAE outcomes. The pooled estimate of TrAE was 1.12 (95% CI 0.70–1.81; I^2 = 93%; P < 0.0001). TrAEs were 0.81 (95% CI 0.37–1.75) with PD-L1/PD-1 monotherapy and 1.34 (95% CI 0.79–2.28) with PD-L1/PD-1 combination therapy [Figure 5]. However, the combination of PD-1inhibitor with higher TrAEs (OR: 2.04, 95% CI 0.66–6.32) [14,25,27,28] than the combination PD-L1inhibitor (OR: 0.95, 95% CI 0.50–1.81) [13,15,22-24].

Subgroup analysis

We performed a subgroup analysis for the ORR and PFS of PD-1/PD-L1 inhibitors according to different factors, as shown in Table 2. When treatment with PD-1/PD-L1 inhibitors was compared to that with active control (sorafenib or lenvatinib) in patients with advanced HCC, the OR of ORR was 3.83 (95% CI 2.42–6.05) and HR of PFS was 0.65 (95% CI 0.54–0.79). Comparison of the use of PD-1/PD-L1

Table 1: Characteristics of included studies

First author/study name	Study registration	Study phase	Line of therapy	Monotherapy or combination therapy	Treatment	Number of patients	ORR, *n* (%)	DCR, *n* (%)	Median PFS, HR	Median OS, HR
Finn 2 *et al*., 2020 [7] (KEYNOTE-240)	NCT02702401	RCT III	Second	Monotherapy	Pembrolizumab	278	51 (18.3)	173 (62.2)	0.72 (0.57–0.90)	0.78 (0.60–1.0)
					Placebo	135	6 (4.4)	72 (53.3)		
Yau *et al*., 2022 [8] CheckMate 459	NCT02576509	RCT III	First	Monotherapy	Nivolumab	371	57 (15.4)	204 (55)	0.93 (0.79–1.09)	0.85 (0.72–1.00)
					Sorafenib	372	26 (7)	216 (58)		
Finn 1 *et al*., 2020 [13] (IMbrave 150)	NCT03434379	RCT III	First	Combination therapy	Atezolizumab + bevacizumab	336	100 (29.8)	247 (73.6)	0.59 (0.44–0.74)	0.58 (0.42–0.80)
					Sorafenib	165	19 (11.3)	88 (53.3)		
Ren *et al*., 2021 [14] (ORIENT-32)	NCT03794440	RCT II/III	First	Combination therapy	Sintilimab + bevacizumab	380	80 (21)	277 (73)	0.56 (0.46–0.70)	0.57 (0.43–0.75)
					Sorafenib	191	8 (4)	120 (63)		
Abou-Alfa *et al*., 2022 and Kudo, 2022 [15,22] (HIMALAYA)	NCT03298451	RCT III	First	Combination therapy	Durvalumab + tremelimumab	393	79 (20.1)	236 (60.1)	0.90 (0.77–1.05)	0.78 (0.62–0.92)
					Sorafenib	389	20 (5.1)	236 (60.7)		
Abou-Alfa *et al*., 2022 and Kudo 2022 [15,22] (HIMALAYA)	NCT03298451	RCT III	First	Monotherapy	Durvalumab	389	66 (17)	213 (54.8)	1.02 (0.88–1.19)	0.86 (0.73–1.03)
					Sorafenib	389	20 (5.1)	236 (60.7)		
Kelley *et al*., 2022 [23]	NCT03755791	RCT III	First	Combination therapy	Atezolizumab + lenvatinib	432	NA	NA	0.63 (0.44–0.91)	0.90 (0.69–1.18)
					Sorafenib	217	NA	NA		
Chen *et al*., 2022 [16]	NA	Retrospective study	First	Combination therapy	Pembrolizumab + lenvatinib	70	NA	NA	0.60 (0.39–0.91)	0.56 (0.38–0.83)
					Lenvatinib	72	NA	NA		
Peng *et al*., 2022 [18]	NA	Retrospective study	Second	Combination therapy	Nivolumab + sorafenib	36	20 (55.6)	23 (63.9)	0.39 (0.19–0.79)	0.36 (0.19–0.70)
					Sorafenib	36	9 (25)	16 (44.4)		
Wu *et al*., 2022 [17]	NA	Retrospective study	First	Combination therapy	Nivolumab + lenvatinib	40	18 (45)	33 (83.5)	NA	NA
					Lenvatinib	47	11 (23.4)	36 (76.6)		
Maesaka *et al*., 2022 [24]	NA	Retrospective study	First	Combination therapy	Atezolizumab + bevacizumab	66	28 (43.8)	49 (76.6)	NA	NA
					Lenvatinib	66	33 (52.4)	52 (82.5)		
He *et al*., 2021 [25]	NA	Retrospective study	Second	Combination therapy	Toripalimab + lenvatinib	71	48 (67.6)	64 (90.1)	0.48 (0.33–0.7)	0.4 (0.24–0.66)
					Lenvatinib	86	14 (16.3)	62 (72.1)		
Xu *et al*., 2021 [26]	NA	Retrospective study	Second	Monotherapy therapy	Toripalimab	53	25 (47.2)	46 (86.8)	0.57 (0.38–0.85)	0.5 (0.31–0.81)
					Lenvatinib	65	6 (9.2)	45 (69.2)		
Wei *et al*., 2021 [27]	NA	Retrospective study	Second	Combination therapy	Camrelizumab + lenvatinib	21	6 (28.6)	15 (71.4)	NA	NA
					Lenvatinib	27	2 (7.4)	14 (51.9)		
Liu *et al*., 2021 [28]	NA	Retrospective study	Second	Combination therapy	Camrelizumab + sorafenib	35	6 (17.1)	24 (68.6)	NA	NA
					Sorafenib	65	2 (3.1)	47 (72.3)		

ORR: Objective response rate, DCR: Disease control rate, HR: Hazard ratio, PFS: Progression-free survival, OS: Overall survival, NA: Not available

inhibitors as first-line therapy versus their use as second-line therapy in patients with advanced HCC showed that their use as second-line therapy in either monotherapy or combination therapy was associated with a higher ORR and PFS than their use as first-line therapy. In this subgroup, we compared PD-1/PD-L1 inhibitor monotherapy with combination therapy. PD-1/PD-L1 inhibitor combination therapy had an advantage in terms of PFS (HR: 0.57 vs. 0.81) compared to that of monotherapy, especially in the second line (HR, 0.46; 95% CI, 0.33–0.64; I^2 = 0%). However, in the subgroup analysis according to the study design, treatment with PD-1/PD-L1 inhibitors had an advantage in terms of ORR (OR: 3.77 vs. 4.02) and PFS (HR: 0.74 vs. 0.53) compared to the control group in both RCTs and retrospective studies.

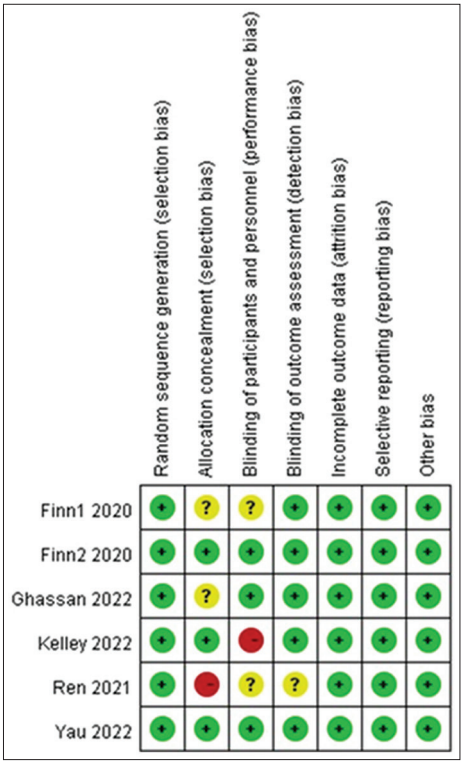

Figure 2: Risk-of-bias assessments for randomized clinical trials included in the meta-analysis

Publication bias

Visual inspection of the ORR funnel plot from these studies revealed asymmetry [Figure 6]. However, neither Egger's nor Begg's tests provided statistical evidence of publication bias, with P = 0.389 and 0.537, respectively.

Discussion

This meta-analysis of six RCTs and eight retrospective studies evaluated 4515 patients with advanced HCC, in both first-and second-line treatments. Patients treated with PD-1/PD-L1 inhibitors showed significantly better ORR, DCR, PFS, and OS than the controls (sorafenib or lenvatinib). Recently, immunotherapy has been proven to be clinically effective for the treatment of advanced HCC. However, no more than 20% of patients with HCC have a strong clinical response to PD-1/PD-L1 inhibitor monotherapy [9,10]. A previous study found that the combination of anti-vascular endothelial growth factor drugs and PD-1/PD-L1 blockade synergistically reverses immunosuppressive microenvironment [29]. Therefore, follow-up studies are moving toward combining PD-1/PD-L1 inhibitors with target agents or combining PD-1/PD-L1 [29]. Although previous meta-analyses targeting PD-1/PD-L1 in advanced HCC have been published [30,31], all these meta-analyses included single-arm phase I/II clinical trials. To date, there have been no meta-analyses of high-quality clinical trials (two- or three-arm trials). In this meta-analysis, we investigated the efficacy and safety of PD-1/PD-L1 inhibitors in patients with HCC by including phase III RCTs and retrospective studies. Based on previous studies and our results, PD-1/PD-L1 inhibitors are promising candidates for HCC treatment. In addition, it was also observed in our study that, compared with PD-1/PD-L1 inhibitor monotherapy, a PD-1/PD-L1 inhibitor combined with target agents achieved a

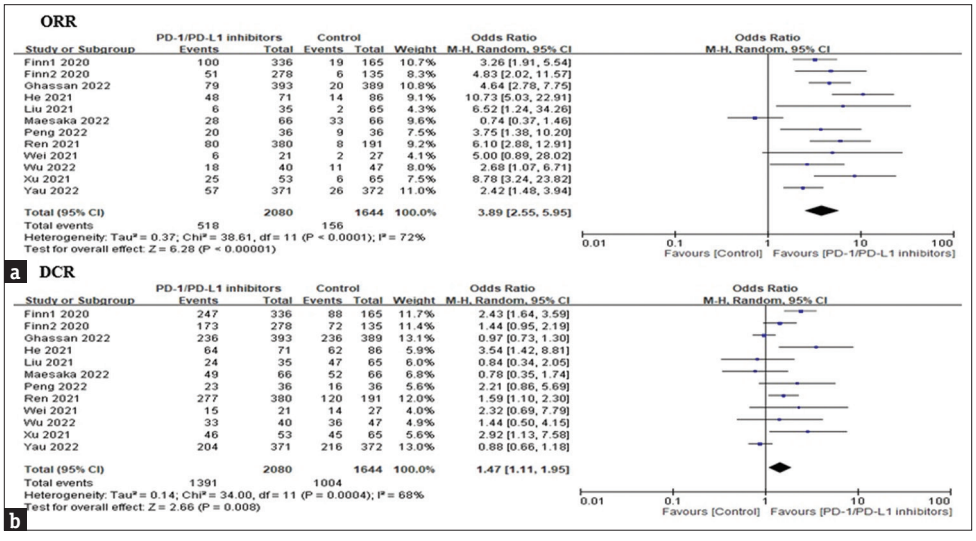

Figure 3: Forest plots for ORR and DCR in patients with advanced hepatocellular carcinoma. (a) ORR, (b) DCR. ORR: Objective response rate, DCR: Disease control rate, CI: Confidence interval

Table 2: Pooled odds ratios and hazard ratios of programmed cell death-1/programmed death ligand 1 treatment on overall response rate and progression-free survival outcomes

	ORR		PFS	
	Pooled OR (95% CI)	Heterogeneity (I^2) (%)	Pooled HR (95% CI)	Heterogeneity (I^2) (%)
Overall	3.89 (2.55–5.95)	72	0.66 (0.56–0.78)	69
Active control	3.83 (2.42–6.05)	74	0.65 (0.54–0.79)	73
Study design				
RCT	3.77 (2.71–5.24)	34	0.74 (0.62–0.88)	69
Retrospective study	4.02 (1.67–9.68)	82	0.53 (0.42–0.65)	0
Line of therapy (monotherapy)				
First-line	3.33 (1.76–6.33)	69	0.91 (0.82–1.02)	0
Second-line	6.26 (3.24–12.07)	0	0.68 (0.55–0.83)	0
Line of therapy (combination therapy)				
First-line	2.85 (1.42–5.72)	82	0.67 (0.54–0.84)	67
Second-line	6.96 (4.06–11.94)	0	0.46 (0.33–0.64)	0
PD-1/PD-L1 inhibitors versus sorafenib or lenvatinib				
Sorafenib	3.70 (2.74–4.98)	18	0.71 (0.57–0.87)	74
Lenvatinib	3.82 (1.19–12.27)	87	0.62 (0.51–0.74)	15
PD-1/PD-L1 inhibitors monotherapy versus combination therapy				
Monotherapy	3.90 (2.41–6.29)	51	0.81 (0.69–0.96)	59
Combination	3.78 (2.19–6.52)	75	0.57 (0.49–0.66)	0

ORR: Objective response rate, PFS: Progression-free survival, RCT: Randomized controlled trial, HR: Hazard ratio, OR: Odds ratio, CI: Confidence interval, PD-1: Programmed cell death-1, PD-L1: Programmed death ligand 1

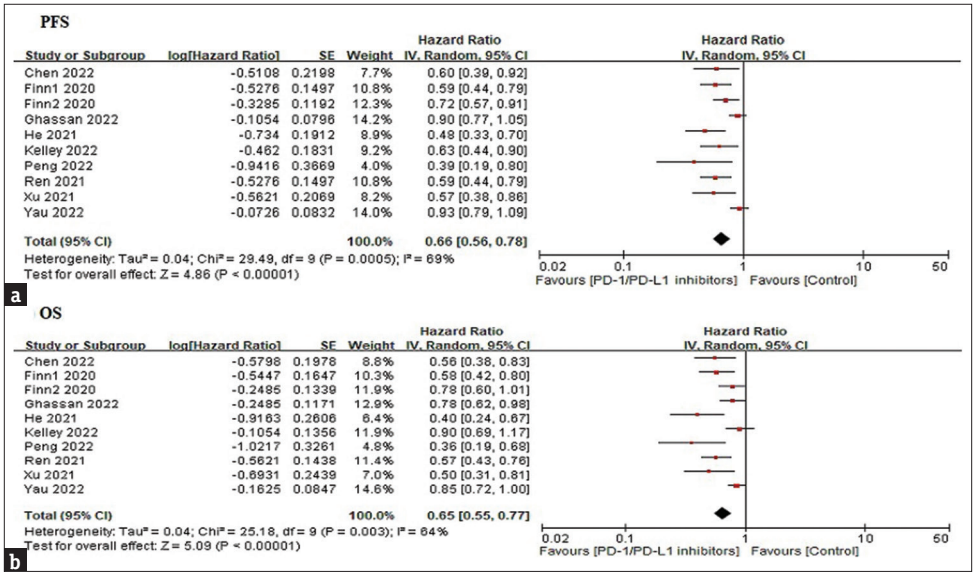

Figure 4: Forest plots for PFS and OS in patients with advanced hepatocellular carcinoma, (a) PFS, (b) OS. PFS: Progression-free survival, OS: Overall survival, CI: Confidence interval

better therapeutic effect and PFS. PD-1/PD-L1 inhibitors can improve immune escape and enhance the antitumor effects of T cells [32].

The occurrence of HCC is driven by abnormal activation of different intracellular pathways, involving the action of tyrosine kinase (TK) protein receptors and non-TK receptors. TK inhibits (TKIs) tumor neovascularization and tumor growth and can inhibit key signaling pathways in the pathogenesis of HCC [33]. TKIs may also have immunomodulatory effects. For example, sorafenib can enhance the activity of tumor-specific effector T-cells and reduce the inhibitory immune cell population. In addition, TKIs can reduce immune escape by inhibiting the expression of PD-L1 on tumor cells [34]. Therefore, the immunomodulatory effect of TKI can enhance the efficacy of anti-PD-1/PD-L1 therapy. Furthermore, combined therapy can be applied to patients with nonresectable HCC. However, durvalumab/tremelimumab is the first dual ICIs containing a combination of anti-PD-L1 and anti-CTLA-4 immunotherapy that has been successfully tested in phase III [15]. Combining anti-PD-1/PD-L1 with anti-CTLA4 therapies was shown to provide additive antitumor activity through its action on the antitumor T-cell response by multiple immune checkpoint blockades [35]. Furthermore, nivolumab in combination with ipilimumab received accelerated approval for the treatment of patients with advanced HCC previously

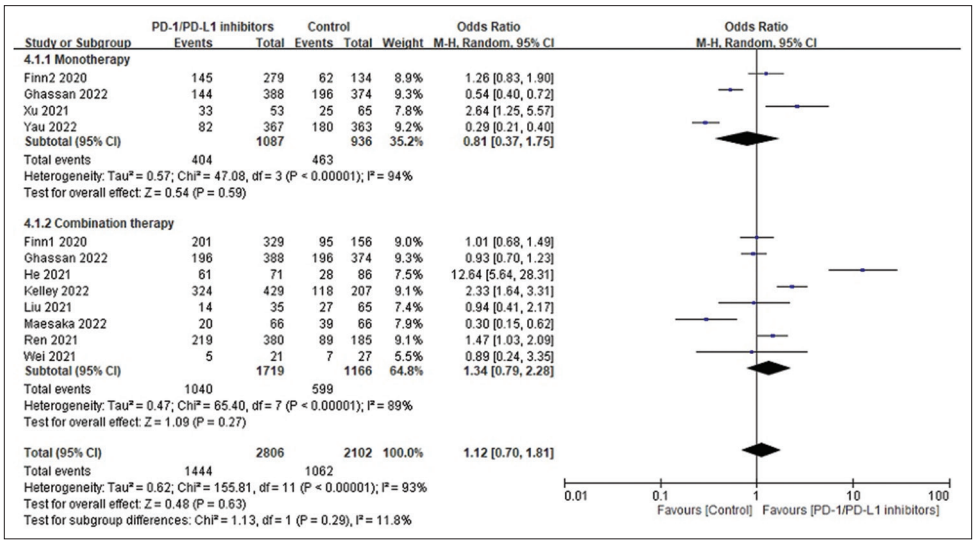

Figure 5: Forest plots for treatment-related adverse events in patients with advanced hepatocellular carcinoma. CI: Confidence interval

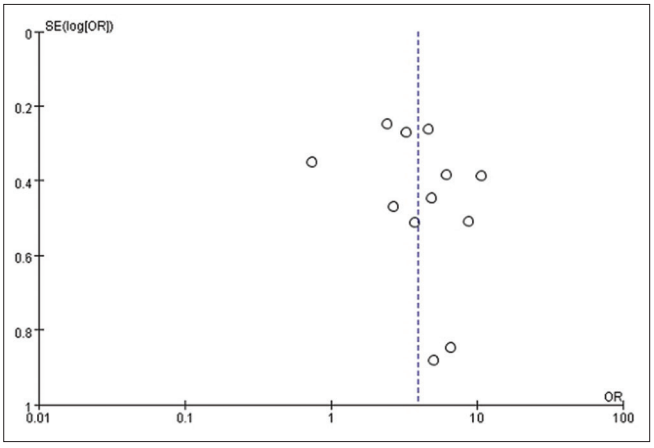

Figure 6: Funnel plot for publication bias for objective response rate

treated with sorafenib based on findings from the phase I/II CheckMate 040 trial [36], and a phase III trial is currently underway.

Our study revealed that PD-1/PD-L1 inhibitors were associated with improved clinical outcomes for patients with advanced HCC. Furthermore, PD-1/PD-L1 inhibitors combination therapy improves clinical outcomes in advanced HCC, both in the first and second lines [Table 2]. However, there is only one phase III study [15] on dual ICIs for advanced HCC that we have included. Dual ICIs for advanced HCC displayed superior efficacy and a favorable benefit-risk profile than sorafenib [15]. ICI-based therapeutic strategies, particularly the combination of ICIs and targeted agents, are promising for the treatment of advanced HCC. However, the optimal treatment strategy and timing of ICI administration in HCC remain challenging.

This meta-analysis had some limitations. First, several retrospective studies that did not report OS and PFS were included. Second, the different study designs and patient populations were significant sources of heterogeneity. Third, the included studies used various targeted agents and PD-1/PD-L1 inhibitors, which may have been biased by varying treatment effects and adverse events between drugs. Fourth, no data were available for cost-effectiveness analysis in these trials. The cost-effectiveness issue for the treatment of HCC is important because of the higher cost of combination therapy than that of monotherapy. Further studies, especially those with cost-effectiveness analyses, are warranted. Despite these limitations, we believe that our research provides the most up-to-date analysis of immunotherapeutic strategies for HCC treatment.

Conclusions

This meta-analysis shows that PD-1/PD-L1 inhibitors are beneficial in the treatment of patients with advanced HCC. The incidence of Grade 3–5 TrAEs with combination therapy was similar to that with the control. However, the incidence of Grade 3–5 TrAEs with PD-1 inhibitor combination therapy was higher than the combination PD-L1 inhibitor. In addition, PD-1/PD-L1 inhibitors in combination with targeted agents and dual immunotherapy resulted in significantly increased PFS compared with that of the control.

Data availability statement

All data, models, and code generated or used during the study appear in the submitted article.

Financial support and sponsorship

This study was supported by grants from the Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (TCRD-TPE-112-50 and TCRD-TPE-112-58).

Conflicts of interest

There are no conflicts of interest.

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.

2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
3. Siegel AB, Olsen SK, Magun A, Brown RS Jr. Sorafenib: Where do we go from here? Hepatology 2010;52:360-9.
4. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627-39.
5. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803-13.
6. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375-84.
7. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: A randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193-202.
8. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): A randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77-90.
9. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
10. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): A non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940-52.
11. Lee DW, Cho EJ, Lee JH, Yu SJ, Kim YJ, Yoon JH, et al. Phase II study of avelumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib. Clin Cancer Res 2021;27:713-8.
12. Voutsadakis IA. PD-1 inhibitors monotherapy in hepatocellular carcinoma: Meta-analysis and systematic review. Hepatobiliary Pancreat Dis Int 2019;18:505-10.
13. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-905.
14. Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): A randomised, open-label, phase 2-3 study. Lancet Oncol 2021;22:977-90.
15. Abou-Alfa GK, Chan SL, Kudo M, Lau G, Kelly RK, Furuse J, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as frst-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. J Clin Oncol 2022;4:379.
16. Chen S, Wu Z, Shi F, Mai Q, Wang L, Wang F, et al. Lenvatinib plus TACE with or without pembrolizumab for the treatment of initially unresectable hepatocellular carcinoma harbouring PD-L1 expression: A retrospective study. J Cancer Res Clin Oncol 2022;148:2115-25.
17. Wu WC, Lin TY, Chen MH, Hung YP, Liu CA, Lee RC, et al. Lenvatinib combined with nivolumab in advanced hepatocellular carcinoma-real-world experience. Invest New Drugs 2022;40:789-97.
18. Peng TR, Wu CC, Chang SY, Chen YC, Wu TW, Hsu CS. Therapeutic efficacy of nivolumab plus sorafenib therapy in patients with unresectable hepatocellular carcinoma. Int Immunopharmacol 2022;112:109223.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
20. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, 2020. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Last accessed on 2023 Sep 01].
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
22. Kudo M. Durvalumab plus tremelimumab in unresectable hepatocellular carcinoma. Hepatobiliary Surg Nutr 2022;11:592-6.
23. Kelley RK, Rimassa L, Cheng AL, Kaseb A, Qin S, Zhu AX, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:995-1008.
24. Maesaka K, Sakamori R, Yamada R, Doi A, Tahata Y, Miyazaki M, et al. Comparison of atezolizumab plus bevacizumab and lenvatinib in terms of efficacy and safety as primary systemic chemotherapy for hepatocellular carcinoma. Hepatol Res 2022;52:630-40.
25. He MK, Liang RB, Zhao Y, Xu YJ, Chen HW, Zhou YM, et al. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. Ther Adv Med Oncol 2021;13:17588359211002720.
26. Xu YJ, Lai ZC, He MK, Bu XY, Chen HW, Zhou YM, et al. Toripalimab combined with hepatic arterial infusion chemotherapy versus lenvatinib for advanced hepatocellular carcinoma. Technol Cancer Res Treat 2021;20:15330338211063848.
27. Wei F, Huang Q, He J, Luo L, Zeng Y. Lenvatinib plus camrelizumab versus lenvatinib monotherapy as post-progression treatment for advanced hepatocellular carcinoma: A short-term prognostic study. Cancer Manag Res 2021;13:4233-40.
28. Liu Q, You N, Li J, Wu K, Peng X, Wang Z, et al. Camrelizumab plus sorafenib versus sorafenib monotherapy for advanced hepatocellular carcinoma: A retrospective analysis. Front Oncol 2021;11:694409.
29. Ma L, Hernandez MO, Zhao Y, Mehta M, Tran B, Kelly M, et al. Tumor cell biodiversity drives microenvironmental reprogramming in liver cancer. Cancer Cell 2019;36:418-30.e6.
30. Rao Q, Li M, Xu W, Pang K, Guo X, Wang D, et al. Clinical benefits of PD-1/PD-L1 inhibitors in advanced hepatocellular carcinoma: A systematic review and meta-analysis. Hepatol Int 2020;14:765-75.
31. Zheng J, Shao M, Yang W, Ren J, Chen X, Yang H. Benefits of combination therapy with immune checkpoint inhibitors and predictive role of tumour mutation burden in hepatocellular carcinoma: A systematic review and meta-analysis. Int Immunopharmacol 2022;112:109244.
32. Reul J, Frisch J, Engeland CE, Thalheimer FB, Hartmann J, Ungerechts G, et al. Tumor-specific delivery of immune checkpoint inhibitors by engineered AAV vectors. Front Oncol 2019;9:52.
33. da Fonseca LG, Reig M, Bruix J. Tyrosine kinase inhibitors and hepatocellular carcinoma. Clin Liver Dis 2020;24:719-37.
34. Wu RY, Kong PF, Xia LP, Huang Y, Li ZL, Tang YY, et al. Regorafenib promotes antitumor immunity via inhibiting PD-L1 and IDO1 expression in melanoma. Clin Cancer Res 2019;25:4530-41.
35. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
36. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: The checkmate 040 randomized clinical trial. JAMA Oncol 2020;6:e204564.