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ORIGINAL RESEARCH

Efficacy and Safety of PD-1/PD-L1 Inhibitors in Advanced Hepatocellular Carcinoma: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have been increasingly employed for the treatment of various cancers in clinical practice. This study aimed to systematically evaluate the efficacy and safety of PD-1/PD-L1 inhibitors for advanced hepatocellular carcinoma (HCC).

Methods: PubMed, EMBASE, Cochrane library, Web of Science, and Abstracts of American Society of Clinical Oncology proceedings databases were searched. Objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), median overall survival (OS), and incidence of adverse events (AEs) and drug withdrawal were pooled. Odds ratio (OR) and hazard ratio (HR) were calculated to analyze the difference in the ORR, DCR, PFS, and OS between groups.

Results: Among the 14,902 initially identified papers, 98 studies regarding use of PD-1/PD-L1 inhibitors in advanced HCC were included. Based on different criteria of response in solid tumors, the pooled ORR, DCR, and median PFS was 16–36%, 54–74%, and 4.5–6.8 months, respectively. The pooled median OS was 11.9 months. Compared to multitarget tyrosine kinase inhibitors (TKIs), PD-1/PD-L1 inhibitors monotherapy significantly increased ORR (OR 2.73, $P < 0.00001$) and OS (HR 0.97, $P = 0.05$), and PD-1/PD-L1 inhibitors combined with TKIs significantly increased ORR (OR 3.17, $P < 0.00001$), DCR (OR 2.44, $P < 0.00001$), PFS (HR 0.58, $P < 0.00001$), and OS (HR 0.58, $P < 0.00001$). The pooled incidence of all-grade AEs, grade ≥ 3 AEs, and drug withdrawal was 71%, 25%, and 7%, respectively.

Conclusion: On the basis of the present systematic review and meta-analysis, PD-1/PD-L1 inhibitors should be the preferred treatment choice for advanced HCC owing to their higher antitumor effect and improved outcomes.

Keywords: PD-1; PD-L1; Objective response rate; Disease control rate; Overall survival; Progression-free survival; Adverse event; Meta-analysis

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Key Summary Points

Why carry out this study?

Evidence regarding use of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors for advanced hepatocellular carcinoma (HCC) has been rapidly growing during recent years.

Therefore, it is necessary to conduct a meta-analysis to examine the efficacy and safety of PD-1/PD-L1 inhibitors in advanced HCC by integrating the currently available data.

What was the hypothesis of the study?

The use of PD-1/PD-L1 might be considered as the first-line choice of treatment for advanced HCC.

What was learned from the study?

Among the patients with advanced HCC treated with PD-1/PD-L1 inhibitors, the disease control rate could be beyond 50%, and the median overall survival time exceeded 1 year, but the incidence of severe adverse events was approximately 25%.

Additionally, PD-1/PD-L1 inhibitor monotherapy and in combination with TKIs were more effective than multitarget TKIs monotherapy for the treatment of advanced HCC.

INTRODUCTION

Primary liver cancer is a major public health burden in the world. According to the global cancer data, primary liver cancer is the sixth most common cancer and the third most common cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) is the dominant subtype of primary liver cancer, accounting for 75–90% [1, 2]. Early and intermediate stage HCC can be effectively treated by liver transplantation, surgical resection, and local ablation [3–5]. Molecular targeted drugs have been successively approved as the first- or second-line choice of therapy for advanced HCC [6–11], but have only a low tumor response rate with a high incidence of adverse events [12, 13].

Since 2015, programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have been explored for the management of advanced HCC [14]. PD-L1 is one of the PD-1 ligands [15]. PD-1 binds to PD-L1, thereby inhibiting the proliferation of T cells [16, 17]. Therefore, PD-1/PD-L1 inhibitors can achieve anticancer effects by inhibiting tumor growth and promoting cancer cell death [18]. Until now, several phase 2 and 3 randomized trials regarding PD-1/PD-L1 inhibitors for the treatment of advanced HCC have been completed with encouraging results [19–21]. Nivolumab and pembrolizumab, which are two major PD-1 inhibitors, have been approved by the US Food and Drug Administration as the second-line treatment options for advanced HCC after the failure of sorafenib in 2017 and 2018, respectively [3–5]. Additionally, atezolizumab, a PD-L1 inhibitor, combined with bevacizumab, a vascular endothelial growth factor receptor monoclonal antibody (anti-VEGFR), has been recommended by the National Comprehensive Cancer Network and American Society of Clinical Oncology (ASCO) guidelines as the first-line treatment for most patients with advanced HCC in 2020 [22, 23]. At present, there is rapidly growing evidence regarding use of PD-1/PD-L1 inhibitors for advanced HCC. Thus, an updated systematic review and meta-analysis is very necessary to integrate all currently available data and further clarify their efficacy and safety.

METHODS

This work was conducted on the basis of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guideline. The PRISMA checklist is shown in Supplementary Table 1. This article is based on previously conducted studies and does not contain any

new studies with human participants or animals performed by any of the authors.

Registration

The PROSPERO registration number is CRD42021264686.

Literature Search

PubMed, EMBASE, Cochrane, Web of Science, and Abstracts of ASCO proceedings databases were searched. Search items were as follows: ("nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "avelumab" OR "cemiplimab" OR "camrelizumab" OR "PD-1/PD-L1" OR "programmed death ligand 1" OR "programmed cell death ligand 1" OR "Opdivo" OR "ONO-4538" OR "MDX-1106" OR "BVMS-936558" OR "Keytruda" OR "MK-3475" OR "MPDL3280A" OR "Tecentriq" OR "RG-7446" OR "MEDI-4736" OR "Mfinzi" OR "IBI-308" OR "SHR-1210") AND ("hepatocellular carcinoma" OR "HCC" OR "liver cell carcinoma" OR "liver cancer" OR "hepatoma" OR "hepatic malignancy" OR "hepatic malignant tumors"). The last search was performed on August 1, 2021.

Study Selection Criteria

Studies regarding use of PD-1/PD-L1 inhibitors in HCC were potentially eligible. Exclusion criteria were as follows: (1) duplicated papers; (2) case reports; (3) reviews and meta-analyses; (4) guidelines and consensus; (5) comments, letters, notes, reports, and editorials; (6) experimental studies; (7) clinical trial registration alone; (8) patients without HCC; (9) patients did not receive PD-1/PD-L1 inhibitors; (10) the sample size was less than 10; (11) overlapping data; and (12) outcomes of interests were neither relevant nor evaluated.

Data Extraction

The data were extracted as follows: first author, publication year, type of publication, study design, region, enrollment period, sample size, PD-1/PD-L1 inhibitors used, dosage of PD-1/PD-L1 inhibitors used, type of drugs combined, follow-up duration, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), 6-month and 1-year PFS, 6-month and 1-year OS, and number of patients who developed all-grade, grade $\geq$ 3 adverse events (AEs), and drug withdrawal secondary to AEs. Notably, among the included studies, ORR, DCR, and PFS were assessed by the independent review committee (IRC) or investigator according to various versions of Response Evaluation Criteria in Solid Tumors (RECIST), such as RECIST version 1.1 (RECIST 1.1), modified RECIST (mRECIST), modified RECIST for immune-based therapeutics (iRECIST), and immune-related RECIST (irRECIST). If a study did not specify whether IRC or investigator assessed the tumor response, it would be considered as the investigator-assessed tumor response.

Quality Assessment

The Cochrane Collaboration's risk of bias tool was used to assess the quality of included randomized controlled trials. Quality assessment items include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias is graded as low, high, or uncertain.

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included cohort studies. Quality assessment items include selection, comparability, exposure, and outcomes. A NOS score of 0–3, 4–6, and 7–9 represents low, moderate, and high quality, respectively.

Data Analyses

The meta-analysis was performed by STATA version 14.2 (STATA Corp, College Station, TX, USA) and Review Manager version 5.3 software (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen). Only a random-effects model was used. First, the ORR, DCR, PFS, and OS were pooled with their 95% confidence

intervals (CIs). Cochrane Q test and the I^2 statistic were used to test the heterogeneity. $P < 0.1$ or $I^2 > 50\%$ represented statistically significant heterogeneity among studies. Meta-regression analyses were employed to explore the source of heterogeneity, where type of publication (full-text vs abstract), study design (prospective vs retrospective), PD-1/PD-L1 inhibitors used (nivolumab vs pembrolizumab vs atezolizumab vs camrelizumab vs durvalumab), median follow-up duration ($\geq$ 10 months vs $<$ 10 months), study quality (high vs moderate and low), sample size ($\geq$ 100 vs $<$ 100), type of PD-1/PD-L1 inhibitors used (PD-1 inhibitors vs PD-L1 inhibitors), type of choice of treatment (monotherapy vs combination therapy), type of drugs combined (anti-VEGFR vs multitarget TKIs vs cytotoxic T lymphocyte-associated antigen 4 [CTLA-4] inhibitors), and region (Asia vs America vs Europe vs multiple countries) were used as covariates. Subgroup analyses were also performed in terms of the covariates aforementioned. Egger's test was performed to evaluate the publication bias, and $P < 0.1$ was considered as statistically significant publication bias. The meta-regression and publication bias analyses were performed when the number of studies included was at least 3. Second, the odds ratio (OR) with 95% CI was pooled to compare ORR and DCR between groups; and the hazard ratio (HR) with 95% CI was pooled to compare PFS and OS between groups. $P < 0.05$ represented statistical significance. Third, the values of incidence of AEs and drug withdrawal with their 95% CIs were pooled.

RESULTS

Study Selection and Characteristics

A total of 14,902 papers were initially identified. Finally, 98 studies were included (Fig. 1). The characteristics of included studies are summarized in Table 1. Among them, 44 studies used PD-1/PD-L1 inhibitor monotherapy [12, 14, 19, 21, 24–63], 60 used combination therapy [20, 39, 45–47, 57, 63–116], and six used both monotherapy and combination therapy [39, 45–47, 57, 63]. Fifty-one studies were published as full-texts [12, 19–21, 24, 26, 30, 34, 35, 37, 39–42, 44–48, 50–52, 54, 56–61, 67–70, 72–74, 76, 78, 80–83, 85, 86, 90, 92, 101, 105–107, 111] and 47 as abstracts [14, 25, 27–29, 31–33, 36, 38, 43, 49, 53, 55, 62–66, 71, 75, 77, 79, 84, 87–89, 91, 93–100, 102–104, 108–110, 112–116]; 58 studies were conducted in Asia [12, 24, 28–31, 36, 39, 40, 44–47, 50, 52, 53, 59, 60, 63–76, 78, 80–86, 88–90, 93, 95–100, 103–106, 108, 111, 114, 115], 8 in America [26, 27, 43, 49, 56, 77, 79, 110], 9 in Europe [32–35, 48, 54, 61, 62, 94], and 27 in multiple countries [14, 19–21, 25, 37, 38, 41, 42, 51, 55, 57, 58, 87, 91, 92, 101, 102, 107, 109, 112, 113, 116]; 81 studies employed PD-1 inhibitors, including pembrolizumab, nivolumab, cemiplimab, camrelizumab, tiselizumab, toripalimab, sintilimab, penpulimab, and CS1003 [12, 14, 19, 21, 24, 26, 27, 29–44, 46–56, 58, 59, 61–71, 73–75, 77–79, 81, 83, 85, 87–106, 108, 109, 111, 113, 115], and 17 employed PD-L1 inhibitors, including durvalumab, avelumab, and atezolizumab [20, 25, 28, 45, 57, 60, 72, 76, 80, 82, 84, 86, 107, 110, 112, 114, 116].

Study Quality

Study quality assessment was summarized in Supplementary Fig. 1 and Supplementary Table 2.

Efficacy of PD-1/PD-L1 Inhibitors Based on Single-Arm Studies

ORR

The pooled ORR was 21% (95% CI 17–24%), 22% (95% CI 19–25%), 29% (95% CI 24–35%), 36% (95% CI 30–42%), and 16% (95% CI 12–20%) according to the IRC-assessed RECIST 1.1, investigator-assessed RECIST 1.1, IRC-assessed mRECIST, investigator-assessed mRECIST, and investigator-assessed iRECIST/irRECIST, respectively (Table 2). The heterogeneity was statistically significant in most of these meta-analyses. The heterogeneity might be related to the choice of treatment

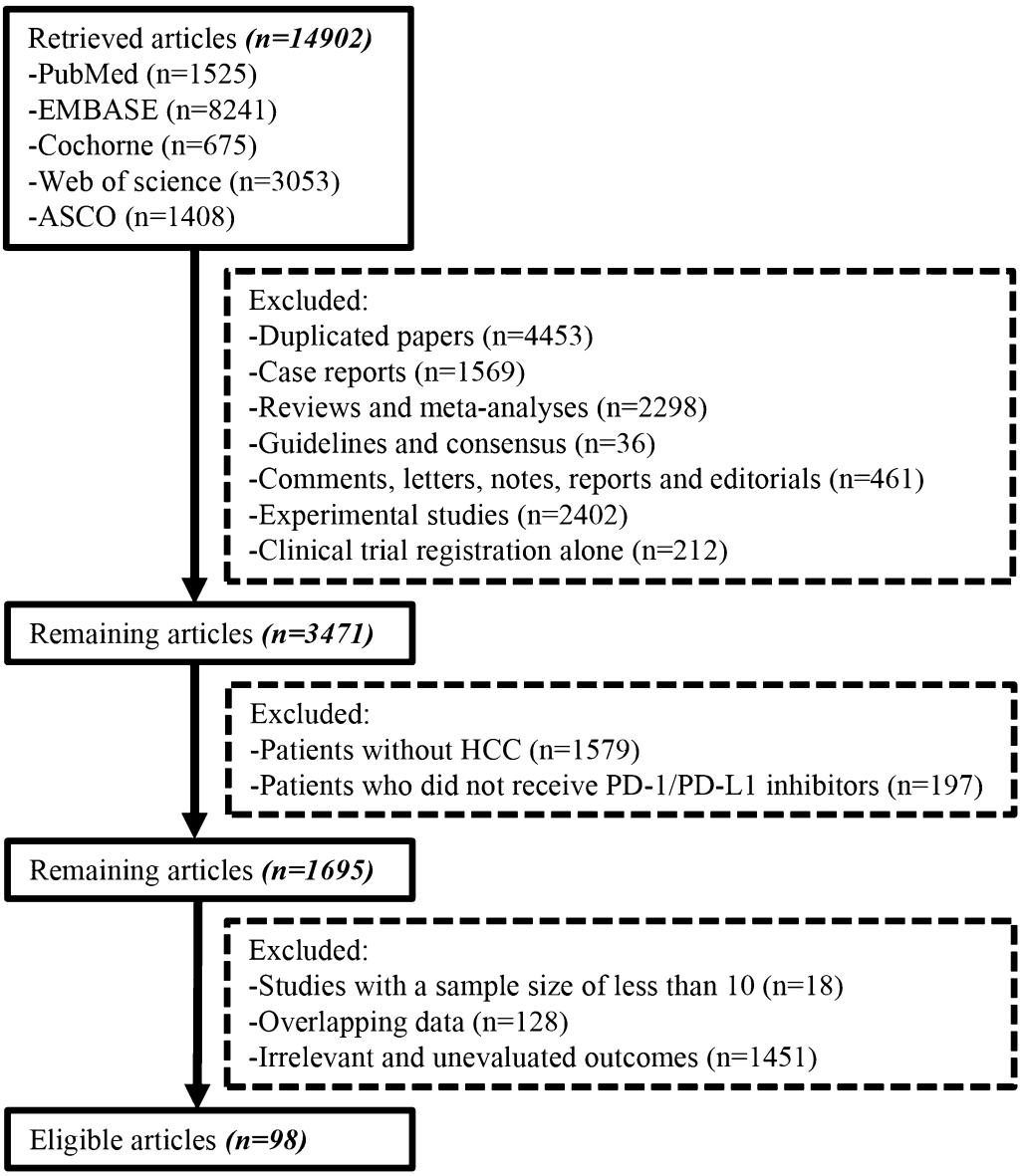

Fig. 1 Flowchart of study selection

(Supplementary Table 3). The interaction according to the choice of treatment was statistically significant in most of the subgroup analyses, suggesting that PD-1/PD-L1 inhibitor combination therapy should have a higher ORR than PD-1/PD-L1 inhibitor monotherapy (Supplementary Table 7). The publication bias was not statistically significant in all of these meta-analyses (Table 2).

DCR

The pooled DCR was 60% (95% CI 52–68%), 66% (95% CI 62–71%), 68% (95% CI 58–78%), 74% (95% CI 68–80%), and 54% (95% CI 43–66%) according to the IRC-assessed RECIST 1.1, investigator-assessed RECIST 1.1, IRC-assessed mRECIST, investigator-assessed mRECIST, and investigator-assessed iRECIST/irRECIST, respectively (Table 2). The heterogeneity was statistically significant in all of these meta-analyses (Table 2). The heterogeneity might be

Table 1 Characteristics of included studies

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Al Jarroudi (2021)	NA	France	Retro cohort	15	Nivolumab (n = 15)	Official dosing	Monotherapy (n = 15)	34
Ducreux (2021)	2018.04–2019.08	Multiple countries	Pro cohort	249	Tislelizumab (n = 249)	200 mg, q3w	Monotherapy (n = 249)	9.1
Gaudel (2021)	2016.01–2019.12	America	Retro cohort	14	Nivolumab (n = 14)	NA	Monotherapy (n = 14)	NA
Kelley (2021)	2015.10–2020.02	Multiple countries	Pro cohort	263	Durvalumab (n = 263)	1500 mg, q4w	Monotherapy (n = 104)	8.9
							Combined with tremelimumab (n = 75)	11.7
							Combined with tremelimumab (n = 84)	14.6
Kudo (2021)	2016.08–2017.01	Multiple countries	Pro cohort	49	Nivolumab (n = 49)	240 mg, q2w	Monotherapy (n = 49)	16.3
Kuo (2021)	2016.07–2019.12	China	Retro cohort	32	Nivolumab (n = 32)	3 mg/kg, q2w	Monotherapy (n = 32)	NA
Lee DW (2021)	2017.12–2019.01	Korea	Pro cohort	30	Avelumab (n = 30)	10 mg/kg, q2w	Monotherapy (n = 30)	13.9
Rimola (2021)	2016.06–2019.02	Spanish	Retro cohort	31	Nivolumab (n = 31)	240 mg or 3 mg/kg, q2w	Monotherapy (n = 31)	8.4
Sardinha (2021)	2017.01–2020.12	Portugal	Retro cohort	26	Nivolumab (n = 26)	NA	Monotherapy (n = 26)	NA
Shi (2021)	2019.06 -NA	China	Pro cohort	48	Toripalimab (n = 48)	240 mg, q3w	Monotherapy (n = 16)	NA
							Combined with ablation (n = 16)	
							Combined with ablation (n = 16)	

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Choi (2020)	2017.07–2019.02	Korea	Retro cohort	150	Nivolumab (n = 150)	3 mg/kg, q2w	Monotherapy (n = 150)	21.4
Chen SX (2020)	2015.01–2019.08	China	Retro cohort	108	Nivolumab (n = 54)	NA	Monotherapy (n = 27)	12.4
					Pembrolizumab (n = 26)		Combined with lenvatinib/ apatinib /sorafenib/ anlotinib (n = 81)	NA
					Others (n = 28)			
Cui (2020)	2015 -2016	China	Retro cohort	55	Nivolumab (n = 36)	1–3 mg/kg or 240 mg, q2w	Monotherapy (n = 55)	13
					Pembrolizumab (n = 13)	2 mg/kg or 200 mg, q3w		
					Penpulimab (n = 6)	200 mg, q3w		
Desai (2020)	2015.05–2017.01	Multiple countries	Pro cohort	50	Tislelizumab (n = 50)	5 mg/kg, q3w	Monotherapy (n = 50)	NA
Fessas (2020)	2017 -2019	Multiple countries	Retro cohort	233	Nivolumab (n = 233)	3 mg/kg, q2w	Monotherapy (n = 233)	8
Finn (2020)	2016.05–2017.11	Multiple countries	RCT	278	Pembrolizumab (n = 278)	200 mg, q3w	Monotherapy (n = 278)	13.8
Garcia (2020)	2012.01–2019.09	America	Retro cohort	30	Nivolumab (n = 30)	NA	Monotherapy (n = 30)	NA
Kim HS (2020)	2012.06–2018.03	America	Retro cohort	261	Nivolumab (n = 261)	NA	Monotherapy (n = 261)	4.5
Lee CH (2020)	2015.07–2018.01	Korea	Retro cohort	48	Nivolumab (n = 48)	3 mg/kg, q2w	Monotherapy (n = 48)	5.2

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Lee MS (2020)	2016.07–2019.03	Multiple countries	Pro cohort	223	Atezolizumab (n = 223)	100 mg, q3w	Combined with bevacizumab (n = 104)	12.4
							Monotherapy (n = 59)	6.7
							Combined with bevacizumab (n = 60)	6.6
Lee PC (2020)	2017.05–2019.08	China	Retro cohort	95	Nivolumab (n = 92)	2–3 mg/kg, q2w;	Monotherapy (n = 82)	5.2
					Pembrolizumab (n = 3)	2–3 mg/kg, q3w	Combined with lenvatinib/sorafenib (n = 13)	NA
Lyu (2020)	2015.07–2017.11	China	Pro cohort	100	Nivolumab	3 mg/kg, q2w	Monotherapy (n = 50)	NA
					Pembrolizumab	3 mg/kg, q3w	Combined with ablation (n = 50)	17.9
Mahn (2020)	2016.05–2019.01	Germany	Retro cohort	14	Nivolumab (n = 10)	3 mg/kg, q2w	Monotherapy (n = 14)	5.2
					Pembrolizumab (n = 4)	200 mg, q3w		
Qin (2020)	2016.11–2017.11	China	Pro cohort	217	Camrelizumab (n = 217)	3 mg/kg, q2w or q3w	Monotherapy (n = 217)	12.5
Spahn (2020)	2015.08–2019.12	Multiple countries	Retro cohort	99	Nivolumab (n = 67)	3 mg/kg, q2w	Monotherapy (n = 99)	16.7
					Pembrolizumab (n = 32)	200 mg, q3w		

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Sung (2020)	2016 -2019	Korea	Retro cohort	33	Nivolumab (n = 33)	3 mg/kg, q2w	Monotherapy (n = 33)	12.5
Wu L (2020)	NA	China	Retro cohort	50	PD-1 inhibitors (n = 50)	NA	Monotherapy (n = 50)	NA
Arora (2019)	NA	India	Retro cohort	35	Nivolumab (n = 35)	3 mg/kg, q2w	Monotherapy (n = 35)	4
Cedillo (2019)	2015.08–2018.01	America	Retro cohort	22	Nivolumab (n = 22)	NA	Monotherapy (n = 22)	NA
Dharmapuri (2019)	2016.06–2018.07	America	Retro cohort	104	Nivolumab (n = 104)	NA	Monotherapy (n = 104)	17
Finkelmeier (2019)	2015.07–2018.01	Germany	Retro cohort	34	Nivolumab (n = 34)	Official dosing	Monotherapy (n = 34)	3.3
Kambhampati (2019)	2015.07–2018.01	America	Retro cohort	18	Nivolumab (n = 18)	3 mg/kg or 240 mg, q2w	Monotherapy (n = 18)	NA
Lin (2019)	2015.08–2018.02	China	Retro cohort	102	Nivolumab (n = 102)	3 mg/kg, q2w	Monotherapy (n = 102)	10.7
Scheiner (2019)	2015.07–2018.12	Multiple countries	Retro cohort	65	Nivolumab (n = 34)	1–3 mg/kg or 240 mg, q2w	Monotherapy (n = 34)	11.2
					Pembrolizumab (n = 31)	2 mg/kg or 200 mg, q3w	Monotherapy (n = 31)	
Yau (2019)	NA	Multiple countries	RCT	371	Nivolumab (n = 371)	240 mg, q2w	Monotherapy (n = 371)	NA
Feun (2018)	2016 -2019	America	Pro cohort	29	Pembrolizumab (n = 29)	200 mg, q3w	Monotherapy (n = 29)	17

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
He AR (2018)	2015.02–2017.09	America	Pro cohort	26	Cemiplimab (n = 26)	3 mg/kg, q2w	Monotherapy (n = 26)	7.2
Shen (2018)	2016.08–2018.04	China	Pro cohort	20	Atezolizumab (n = 20)	1200 mg, q3w	Monotherapy (n = 20)	10.6
Yoon (2018)	2017.03–2018.05	Korea	Retro cohort	76	Nivolumab (n = 76)	3 mg/kg or < 3 mg/kg, q2w	Monotherapy (n = 76)	3.8
Zhu (2018)	2016.06–2017.02	Multiple countries	Pro cohort	104	Pembrolizumab (n = 104)	200 mg, q3w	Monotherapy (n = 104)	12.3
El-Khoueiry (2017)	2012.11–2016.08	Multiple countries	Pro cohort	262	Nivolumab (n = 262)	0.1–10 mg/kg, q2w 3 mg/kg, q2w	Monotherapy (n = 48) Monotherapy (n = 214)	NA
Feng (2017)	2016.01–2017.01	China	Retro cohort	11	Nivolumab (n = 11)	3 mg/kg, q3w	Monotherapy (n = 11)	NA
Wainberg (2017)	2012.09–2016.01	Multiple countries	Pro cohort	40	Durvalumab (n = 40)	10 mg/kg, q2w	Monotherapy (n = 40)	6
El-Khoueiry (2015)	2012.10 -NA	Multiple countries	Pro cohort	41	Nivolumab (n = 41)	0.1–10 mg/kg, q2w	Monotherapy (n = 41)	6
Ando (2021)	2020.09–2021.03	Japan	Retro cohort	40	Atezolizumab (n = 40)	1200 mg, q3w	Combined with bevacizumab (n = 40)	4
Chen S (2021)	2016.06–2020.06	Korea	Retro cohort	70	Pembrolizumab (n = 70)	200 mg, q3w	Combined with lenvatinib and TACE (n = 70)	27
Cheon (2021)	2020.05–2021.02	Korea	Retro cohort	121	Atezolizumab (n = 121)	1200 mg, q3w	Combined with bevacizumab (n = 121)	5.9
Han (2021)	2019.01–2019.09	China	Pro cohort	31	Penpulimab (n = 31)	200 mg, q3w	Combined with anlotinib (n = 31)	15.2

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Hayakawa (2021)	2020.10–2021.04	Japan	Retro cohort	52	Atezolizumab (n = 52)	1200 mg, q3w	Combined with bevacizumab (n = 52)	4.2
He MK (2021)	2019.02–2019.08	China	Retro cohort	71	Toripalimab (n = 71)	240 mg, q3w	Combined with lenvatinib and HAIC (n = 71)	NA
Hiraoka (2021)	2020.09–2021.04	Japan	Retro cohort	171	Atezolizumab (n = 171)	1200 mg, q3w	Combined with bevacizumab (n = 171)	2.3
Huang (2021)	2019.01–2019.12	China	Retro cohort	13	Camrelizumab (n = 13)	200 mg, q3w	Combined with sorafenib and TACE (n = 13)	19
Hsiehchen (2021)	2018.04 -NA	America	Pro cohort	18	Pembrolizumab (n = 18)	200 mg, q3w	Combined with bevacizumab (n = 18)	NA
Kudo (2021)	2017.09–2018.01	Japan	Pro cohort	22	Avelumab (n = 22)	10 mg/kg, q2w	Combined with axitinib (n = 22)	18
Kim RD (2021)	2018.06–2020.07	America	Pro cohort	16	Pembrolizumab (n = 16)	200 mg, q3w	Combined with regorafenib (n = 16)	NA
Lee IC (2021)	NA	Korea	Retro cohort	62	Pembrolizumab (n = 62)	200 mg, q3w	Combined with lenvatinib (n = 62)	8
Mei (2021)	2018.11–2019.12	China	Retro cohort	81	Nivolumab (n = 3)	100 mg	Combined with HAIC (n = 81)	11
					Pembrolizumab (n = 4)	200 mg		
					Toripalimab (n = 49)	240 mg		
					Sintilimab (n = 28)	200 mg		

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Mei (2021)	2018.07–2019.12	China	Retro cohort	70	Nivolumab (n = 7)	100 mg	Combined with lenvatinib and HAIC (n = 45)	15.1
					Pembrolizumab (n = 11)	200 mg		
					Toripalimab (n = 53)	240 mg	Combined with lenvatinib (n = 25)	
					Sintilimab (n = 7)	200 mg		
Ohki (2021)	NA	Japan	Retro cohort	20	Atezolizumab (n = 20)	1200 mg, q3w	Combined with bevacizumab (n = 20)	NA
Sum (2021)	NA	China	Retro cohort	25	Nivolumab Pembrolizumab	NA	Combined with ipilimumab (n = 25)	37.7
Wei (2020)	2019.06–2020.03	China	Retro cohort	21	Camrelizumab (n = 21)	200 mg, q3w	Combined with lenvatinib (n = 21)	8.4
Wong (2021)	2016.06–2020.02	China	Retro cohort	25	Nivolumab (n = 12)	3 mg/kg, q3w	Combined with ipilimumab (n = 25)	37.7
					Pembrolizumab (n = 13)	2 mg/kg, q3w		
Xie (2021)	2019.02–2019.12	China	Retro cohort	60	Sintilimab (n = 60)	200 mg, q3w	Combined with lenvatinib/ apatinib /sorafenib/ regorafenib (n = 60)	10.4
Xu (2021)	2018 -2019	China	Pro cohort	190	Camrelizumab (n = 190)	200 mg (BW > 50 kg) or 3 mg/kg (BW < 50 kg), q2w	Combined with apatinib (n = 190)	15.4

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Zeng Y (2021)	2020.03–2020.12	China	Pro cohort	41	Camrelizumab (n = 41)	200 mg, q2w	Combined with lenvatinib/ apatinib /sorafenib/ regoraenib (n = 41)	5.3
Zeng Z (2021)	2019.03–2020.12	China	Retro cohort	45	Sintilimab (n = 45)	200 mg, q3w	Combined with sorafenib (n = 29)	NA
							Combined with lenvatinib (n = 16)	
Zhang T (2021)	NA	China	Retro cohort	34	Camrelizumab	200 mg, q3w	Combined with lenvatinib/ apatinib /sorafenib/HAIC (n = 34)	9.7
Bang (2020)	2015.09–2017.09	Multiple countries	Pro cohort	28	Durvalumab (n = 28)	750 mg, q2w	Combined with ramucirumab (n = 28)	20
Chen C (2020)	2017.07–2019.06	China	Retro cohort	22	Nivolumab (n = 22)	3 mg/kg, q3w	Combined with lenvatinib/sorafenib/ regorafenib (n = 15)	8.8
							Combined with chemotherapy (n = 7)	
Chen JZ (2020)	2018.11–2020.06	China	Retro cohort	37	Toripalimab (n = 23)	3 mg/kg or 240 mg, q2w	Combined with surgery/ radiation/ HAIC/TACE/ apatinib (n = 37)	14.8
					Sintilimab (n = 14)	200 mg, q3w		12.3
Chen X (2020)	2019.06–2020.06	China	Pro cohort	16	Sintilimab (n = 16)	200 mg, q3w	Combined with anlotinib (n = 16)	5.3
Chen Y (2020)	2018.10–2019.01	China	Retro cohort	26	Pembrolizumab (n = 26)	NA	Combined with lenvatinib (n = 26)	NA

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
El-Khoueiry (2020)	2018.06–2019.08	Multiple countries	Pro cohort	29	Pembrolizumab (n = 29)	200 mg, q3w	Combined with regorafenib (n = 29)	NA
Finn (2020)	2018.03–2019.09	Multiple countries	RCT	336	Atezolizumab (n = 336)	1200 mg, q3w	Combined with bevacizumab (n = 336)	8.9
Finn (2020)	2017.02–2019.04	Multiple countries	Pro cohort	104	Pembrolizumab (n = 104)	200 mg, q3w	Combined with lenvatinib (n = 104)	10.6
Jia (2020)	2019.02–2020.02	China	Pro cohort	24	Sintilimab (n = 24)	200 mg, q3w	Combined with bevacizumab (n = 24)	9
Kudo (2020)	2018.01–2019.05	Japan	Pro cohort	30	Nivolumab (n = 30)	240 mg, q2w	Combined with lenvatinib (n = 30)	NA
Li (2020)	2018.11–2019.11	China	Retro cohort	22	PD-1 inhibitors (n = 22)	NA	Combined with lenvatinib (n = 22)	6.6
Ren (2020)	2019.02–2020.08	China	RCT	380	Sintilimab (n = 380)	200 mg, q3w	Combined with bevacizumab (n = 380)	10
Shen (2020)	2018.10–2020.03	China	Pro cohort	19	CS1003 (n = 19)	200 mg, q3w	Combined with lenvatinib (n = 19)	NA
Sun (2020)	2018.09–2020.01	China	Retro cohort	59	Nivolumab Pembrolizumab Camrelizumab Sintilimab Toripalimab	NA	Combined with lenvatinib (n = 59)	NA
Tai (2020)	NA	Singapore	Pro cohort	36	Nivolumab (n = 36)	240 mg, q2w	Combined with TARE (n = 36)	16.4

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Wu CJ (2020)	2019.07 -NA	China	Pro cohort	45	Pembrolizumab (n = 45)	100 mg, q3w	Combined with lenvatinib (n = 45)	5.2
Yau (2020)	2016 -2019	Multiple countries	Pro cohort	71	Nivolumab (n = 71)	240 mg, q2w	Combined with cabozantinib (n = 36)	NA
						3 mg/kg, q2w	Combined with cabozantinib and ipilimumab (n = 35)	
Yau (2020)	2016.01–2016.09	Multiple countries	RCT	148	Nivolumab (n = 50)	1 mg/kg, q3w followed by 240 mg, q2w;	Combined with ipilimumab (n = 148)	30.7
					Nivolumab (n = 49)	3 mg/kg, q3w followed by 240 mg, q2w;		
					Nivolumab (n = 49)	3 mg/kg, q3w		
Yuan (2020)	2019.01–2020.07	China	Retro cohort	63	Camrelizumab (n = 63)	200 mg, q3w	Combined with apatinib (n = 63)	12.6
Zhang W (2020)	Till 2020.05	China	Pro cohort	33	Pembrolizumab	200 mg, q3w	Combined with lenvatinib (n = 33)	7.2
					Sintilimab	200 mg, q3w		
					Toripalimab	240 mg, q3w		
Zhang W (2020)	2018.10–2020.01	China	Pro cohort	50	Sintilimab (n = 50)	200 mg, q3w	Combined with bevacizumab (n = 50)	NA
Zhu (2020)	2017.02–2019.01	Multiple countries	Pro cohort	104	Pembrolizumab (n = 104)	200 mg, q3w	Combined with lenvatinib (n = 104)	10.6
Floudas (2019)	NA	America	Pro cohort	10	Durvalumab (n = 10)	1500 mg, q4w	Combined with tremelimumab (n = 10)	NA

Table 1 continued

First author (year)	Enrollment period	Country	Study design	No	PD-1/PD-L1 inhibitors used	Dosage	Choice of treatment	Median follow-up duration (months)
Llovet (2019)	2017.12–2018.12	Multiple countries	Pro cohort	67	Pembrolizumab (n = 67)	200 mg, q3w	Combined with lenvatinib (n = 67)	11.7
Qin (2019)	2017.04–2018.01	China	Pro cohort	34	Camrelizumab (n = 34)	3 mg/kg, q2w	Combined with FOLFOX4/ GEMOX (n = 34)	NA
Cheng (2018)	NA	Japan	Pro cohort	20	Atezolizumab (n = 20)	1200 mg, q3w	Combined with codrituzumab (n = 20)	NA
Chen SC (2018)	NA	China	Retro cohort	43	Nivolumab (n = 43)	3 mg/kg, q2w	Combined with sorafenib (n = 43)	NA
Pishvaian (2018)	2016.04–2018.07	Multiple countries	Pro cohort	68	Atezolizumab (n = 68)	1200 mg, q3w	Combined with bevacizumab (n = 68)	NA
Xu (2018)	2016.10–2018.02	China	Pro cohort	18	Camrelizumab (n = 18)	200 mg, q3w	Combined with apatinib (n = 18)	7.8
Ikeda (2018)	2017.02–2017.12	Multiple countries	Pro cohort	18	Pembrolizumab (n = 18)	200 mg, q3w	Combined with Lenvatinib (n = 18)	NA
Kelley (2017)	2015.10–2017.01	Multiple countries	Pro cohort	40	Durvalumab (n = 40)	20 mg/kg, q4w	Combined with tremelimumab (n = 40)	NA

Pro prospective, *Retro* retrospective, *RCT* randomized controlled trial, *BW* body weight, *TACE* transcatheter arterial chemoembolization, *TRAE* transarterial radioembolization, *HAIC* hepatic artery infusion chemotherapy, *FOLFOX4* fluorouracil, leucovorin, and oxaliplatin, *GEMOX* gemcitabine and oxaliplatin, *NA* not available

related to the choice of treatment (Supplementary Table 4). The interaction according to the choice of treatment was statistically significant in all of subgroup analyses, suggesting that PD-1/PD-L1 inhibitor combination therapy should have a higher DCR than PD-1/PD-L1 inhibitor monotherapy (Supplementary Table 7). The publication bias was not statistically significant in most of these meta-analyses.

PFS

The pooled median PFS was 4.5 months (95% CI 3.6–5.4), 5.6 months (95% CI 4.6–6.6), 6.3 months (95% CI 4.0–8.6), 6.8 months (95% CI 4.6–9.0), and 5.7 months (95% CI 3.8–7.5) according to the IRC-assessed RECIST 1.1, investigator-assessed RECIST 1.1, IRC-assessed mRECIST, investigator-assessed mRECIST, and investigator-assessed iRECIST/irRECIST, respectively (Table 2). The pooled 6-month PFS rate was 60% (95% CI 54–67%), 51% (95% CI 42–60%), 60% (95% CI 50–0.70%), and 52% (95% CI 41–63%) according to the IRC-assessed RECIST 1.1, investigator-assessed RECIST 1.1, IRC-assessed mRECIST, and investigator-assessed mRECIST, respectively. The pooled 1-year PFS rate was 27% (95% CI 20–37%), 24% (95% CI 14–36%), 28% (95% CI 22–34%), and 34% (95% CI 24–41%) according to the IRC-assessed RECIST 1.1, investigator-assessed RECIST 1.1, IRC-assessed mRECIST, and investigator-assessed mRECIST, respectively. The heterogeneity was statistically significant in most of these meta-analyses (Table 2). The heterogeneity might be related to the choice of treatment (Supplementary Table 5). The interaction according to the choice of treatment was statistically significant in most of the subgroup analyses, suggesting that PD-1/PD-L1 inhibitor combination therapy should have a higher PFS than PD-1/PD-L1 inhibitor monotherapy (Supplementary Table 7). The publication bias was not statistically significant in all of these meta-analyses (Table 2).

OS

The pooled median OS was 11.9 months (95% CI 10.6–13.2). The pooled 6-month and 1-year OS rates were 82% (95% CI 76–88%) and 58% (95% CI 52–64%), respectively. The heterogeneity was statistically significant in all of these meta-analyses (Table 2). The heterogeneity might be related to the choice of treatment in most of the meta-regression analyses (Supplementary Table 6). The interaction according to the choice of treatment was statistically significant in all of subgroup analyses, suggesting that PD-1/PD-L1 inhibitor combination therapy should have a higher OS than PD-1/PD-L1 inhibitor monotherapy (Supplementary Table 7). The publication bias was statistically significant in the meta-analyses regarding median OS, but not those regarding 6-month OS and 1-year OS rates (Table 2).

Efficacy of PD-1/PD-L1 Inhibitor Monotherapy Versus Multitarget TKIs Monotherapy

Four studies compared the efficacy of PD-1/PD-L1 inhibitor monotherapy versus multitarget TKIs monotherapy (Table 3). Nivolumab was the only PD-1/PD-L1 inhibitors drug used among these studies. Meta-analyses showed that nivolumab monotherapy significantly increased ORR (OR 2.73, 95% CI 1.87–3.98, $P < 0.00001$) and OS (HR 0.72, 95% CI 0.52–1.00, $P = 0.05$). The heterogeneity was statistically significant in the meta-analysis regarding OS, but not that regarding ORR (Fig. 2).

Efficacy of PD-1/PD-L1 Inhibitors Combined with TKIs Versus Multitarget TKIs Monotherapy

Five studies compared the efficacy of PD-1/PD-L1 inhibitors combined with TKIs versus multitarget TKIs monotherapy (Table 3). Meta-analyses showed that PD-1/PD-L1 inhibitors combined with TKIs significantly increased ORR (OR 3.17, 95% CI 2.21–4.54, $P < 0.00001$), DCR (OR 2.44, 95% CI 1.74–3.44, $P < 0.00001$), PFS (HR 0.58, 95% CI 0.50–0.68, $P < 0.00001$), and OS (HR 0.58, 95% CI 0.49–0.70, $P < 0.00001$). The heterogeneity was not statistically significant in all of these meta-analyses (Fig. 3).

Table 2 Results of meta-analyses regarding ORR, DCR, PFS, and OS

Outcomes and criteria	No. studies	Effect size (95% CI)	Heterogeneity		Publication bias
			I^2 (%)	*P* value	*P* value
ORR					
IRC-assessed RECIST 1.1	17	0.21 (0.17–0.24)	82.8	< 0.01	0.917
Investigator-assessed RECIST 1.1	63	0.22 (0.19–0.25)	74.8	< 0.01	0.577
IRC-assessed mRECIST	8	0.29 (0.24–0.35)	77.3	< 0.01	0.244
Investigator-assessed mRECIST	36	0.36 (0.30–0.42)	86.3	< 0.01	0.961
Investigator-assessed iRECIST/irRECIST	8	0.16 (0.12–0.20)	0.0	0.55	0.911
DCR					
IRC-assessed RECIST 1.1	13	0.60 (0.52–0.68)	92.4	< 0.01	0.976
Investigator-assessed RECIST 1.1	57	0.66 (0.62–0.71)	83.7	< 0.01	0.622
IRC-assessed mRECIST	7	0.68 (0.58–0.78)	91.3	< 0.01	*0.026*
Investigator-assessed mRECIST	36	0.74 (0.68–0.80)	87.2	< 0.01	0.455
Investigator-assessed iRECIST/irRECIST	5	0.54 (0.43–0.66)	72.6	< 0.01	*0.011*
Median PFS					
IRC-assessed RECIST 1.1	12	4.5 (3.6–5.4)	95.5	< 0.01	0.501
Investigator-assessed RECIST 1.1	26	5.6 (4.6–6.6)	87.6	< 0.01	0.421
IRC-assessed mRECIST	4	6.3 (4.0–8.6)	91.0	< 0.01	0.187
Investigator-assessed mRECIST	11	6.8 (4.6–9.0)	96.4	< 0.01	0.470
Investigator-assessed iRECIST/irRECIST	2	5.7 (3.8–7.5)	10.8	0.29	–
6-month PFS					
IRC-assessed RECIST 1.1	5	0.60 (0.54–0.67)	58.4	0.05	0.603
Investigator-assessed RECIST 1.1	12	0.51 (0.42–0.60)	76.3	< 0.01	0.621
IRC-assessed mRECIST	1	0.60 (0.50–0.70)	–	–	–
Investigator-assessed mRECIST	7	0.52 (0.41–0.63)	81.4	< 0.01	0.433
1-year PFS					
IRC-assessed RECIST 1.1	4	0.27 (0.20–0.37)	71.1	< 0.01	0.160
Investigator-assessed RECIST 1.1	3	0.24 (0.14–0.36)	42.9	0.17	0.744
IRC-assessed mRECIST	2	0.28 (0.22–0.34)	0.0	0.54	–
Investigator-assessed mRECIST	5	0.34 (0.24–0.41)	60.5	< 0.01	0.746
Median OS	30	11.9 (10.6–13.2)	93.3	< 0.01	*0.025*
6-month OS	17	0.82 (0.76–0.88)	87.6	< 0.01	0.746

Table 2 continued

Outcomes and criteria	No. studies	Effect size (95% CI)	Heterogeneity		Publication bias
			I^2 (%)	*P* value	*P* value
1-year OS	23	0.58 (0.52–0.64)	86.3	< 0.01	0.783

ORR objective response rate, *DCR* disease control rate, *PFS* progression-free survival, *OS* overall survival, *CI* confidence interval, *IRC* independent review committee, *RECIST* Response Evaluation Criteria in Solid Tumors, *mRECIST* modified Response Evaluation Criteria in Solid Tumors, *iRECIST* modified RECIST for immune based therapeutics, *irRECIST* immune-related Response Evaluation Criteria in Solid Tumors

Table 3 Outcomes: a summary of comparative studies

First author (year)	Groups	No. Pts	ORR	DCR	PFS (months) (95% CI)	OS (months) (95% CI)
Kuo (2021)	Nivolumab	32	15.6%	43.8%	NA	14.0
	Regorafenib	58	6.4%	31.9%	NA	11.0
Choi (2020)	Nivolumab	150	13.3%	39.3%	1.8 (1.6–2.5)	8.2 (5.4–10.6)
	Regorafenib	223	4.0%	46.6%	3.0 (2.3–3.3)	7.7 (7.2–8.9)
Lee CH (2020)	Nivolumab	48	16.7%	50.0%	NA	5.9 (3.2–18.1)
	Regorafenib	102	5.9%	47.1%	NA	6.9 (3.5–13.1)
Yau (2019)	Nivolumab	371	15.4%	NA	3.7 (3.1–3.9)	16.4 (13.9–18.4)
	Sorafenib	372	7.0%	NA	3.8 (3.7–4.5)	14.7 (11.9–17.2)
Lee IC (2021)	Pembrolizumab + lenvatinib	62	58.1%	85.5%	8.4	NA
	Lenvatinib	61	32.8%	62.3%	4.9	17.2
Wei (2021)	Camrelizumab + lenvatinib	21	28.6%	71.4%	8.0	NA
	Lenvatinib	27	7.4%	51.9%	4.0	NA
Finn (2020)	Atezolizumab + bevacizumab	326	27.3%	73.6%	6.8 (5.7–8.3)	NA
	Sorafenib	165	11.9%	55.3%	4.3 (4.0–5.6)	13.2 (10.4–NA)
Li (2020)	PD-1 inhibitors + lenvatinib	22	45.5%	90.9%	NA	NA
	Lenvatinib	22	18.2%	77.3%	NA	NA
Ren (2020)	Sintilimab + bevacizumab	364	20.3%	NA	4.5	NA
	Sorafenib	122	5.7%	NA	2.8	10.4

ORR objective response rate, *DCR* disease control rate, *PFS* progression-free survival, *OS* overall survival, *CI* confidence interval, *NA* not available, *Pts* patients

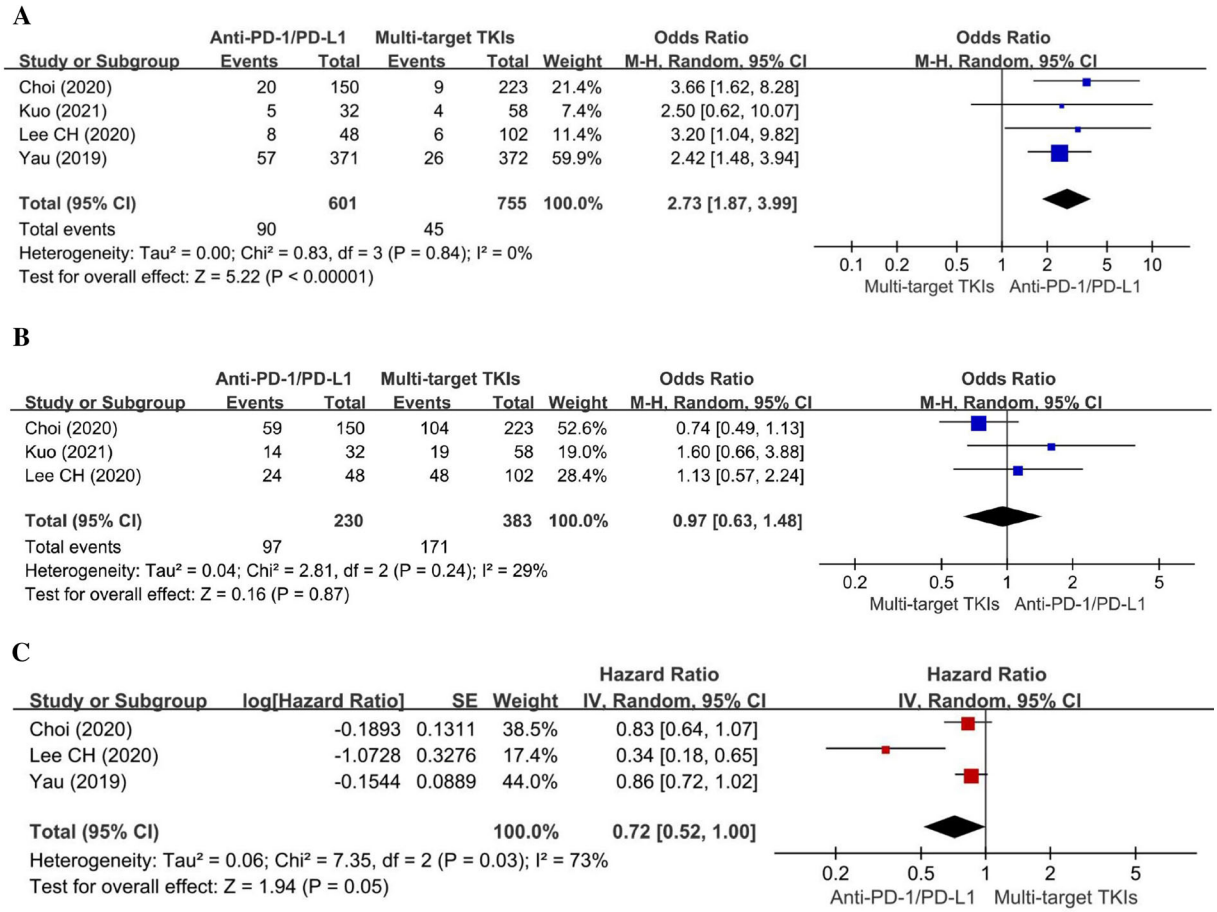

Fig. 2 Comparison of tumor response rate and survival time between PD-1/PD-L1 inhibitor monotherapy and multitarget TKIs monotherapy groups. **a** ORR; **b** DCR; **c** OS

Safety

All-Grade AEs

The pooled rate of all-grade AEs was 71% (95% CI 64–77%) with significant heterogeneity (I^2 = 94.0%, $P < 0.01$) (Supplementary Table 8). The most common all-grade AEs was hypertension (23%) and hand-foot syndrome (23%), followed by fatigue (20%), proteinuria (20%), and reactive cutaneous capillary endothelial proliferation (RCCEP) (19%) (Supplementary Table 9).

Grade ≥ 3 AEs

The pooled grade ≥ 3 AEs rate was 25% (95% CI 21–30%) with significant heterogeneity (I^2 = 91.3%, $P < 0.01$) (Supplementary Table 8). The most common grade ≥ 3 AEs was hypertension (7%), followed by increased aspartate aminotransferase (AST) level (6%), hepatitis (6%), increased gamma-glutamyltransferase level (4%), and increased lipase level (4%) (Supplementary Table 9).

AE-Related Drug Withdrawal

The pooled incidence of drug withdrawal due to AEs was 7% (95% CI 6–9%) with significant heterogeneity (I^2 = 69.6%, $P < 0.01$) (Supplementary Table 8).

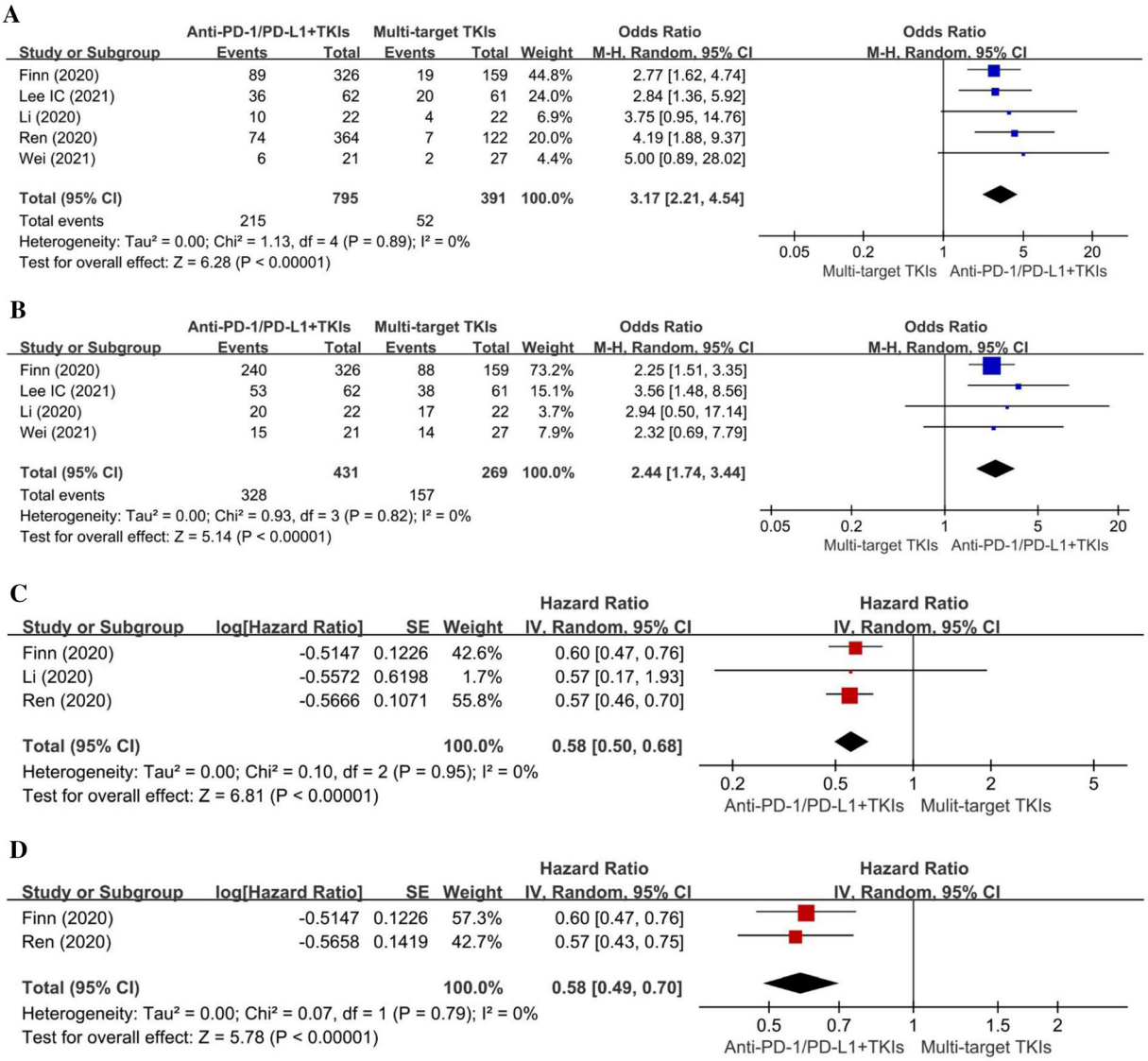

Fig. 3 Comparison of tumor response rate and survival time between PD-1/PD-L1 inhibitors combined with multitarget TKIs therapy and multitarget TKIs monotherapy groups. **a** ORR; **b** DCR; **c** PFS; **d** OS

DISCUSSION

To the best of our knowledge, this is the most comprehensive systematic review and meta-analysis to verify the efficacy and safety of PD-1/PD-L1 inhibitors for advanced HCC. Major findings are as follows: (1) PD-1/PD-L1 inhibitors can achieve an ORR of 16–36%, DCR of 54–74%, median PFS of 4.5–6.8 months, and median OS of 11.9 months in patients with advanced HCC; (2) PD-1/PD-L1 inhibitor monotherapy and in combination with TKIs therapy outperform multitarget TKIs monotherapy in terms of ORR, PFS, and OS; (3) one in four patients with advanced HCC treated with PD-1/PD-L1 inhibitors develop severe AEs, but only 7% of them discontinue therapy because of severe AEs.

It should be acknowledged that two previous systematic reviews and meta-analyses explored

the efficacy and safety of PD-1/PD-L1 inhibitors for advanced HCC [117, 118]. By comparison, our present meta-analysis had some advantages. First, the most important was to compare the efficacy of PD-1/PD-L1 inhibitors versus multitarget TKIs monotherapy for the treatment of advanced HCC, which had not been performed by previous meta-analyses [117, 118]. Second, one previous meta-analysis searched literature until January 2020 and included 23 studies [118]. Another previous meta-analysis searched literature until October 2020 and included only 12 studies [117]; therefore, some eligible studies were missing [27–29, 31, 32, 36, 38, 110, 113, 115, 116]. By comparison, our present meta-analysis extended the date of literature search until August, 2021 and finally included 98 studies. Third, two previous meta-analyses extracted the data based on only one criterion of response evaluation in solid tumors [117, 118]. By comparison, our present meta-analysis pooled the data according to five different criteria of response evaluation in solid tumors. Notably, we found that the pooled ORR, DCR, and PFS assessed by investigators according to the mRECIST were higher than those according to other criteria. This may be because mRECIST is more specific for evaluation of HCC, and can objectively and accurately evaluate the ORR, DCR, and PFS in trials of non-cytotoxic drugs for HCC [119, 120]. Fourth, the heterogeneity was statistically significant in both previous and present meta-analyses. The source of heterogeneity was not explored in two previous meta-analyses [117, 118]. By comparison, we explored the source of heterogeneity by subgroup and meta-regression analyses, and found that the heterogeneity might be related to the choice of treatment. More specifically, our subgroup analyses indicated that PD-1/PD-L1 inhibitor combination therapy had a higher tumor response rate and longer survival time than PD-1/PD-L1 inhibitor monotherapy. This is because PD-1/PD-L1 inhibitors combined with other treatment approaches, such as anti-VEGFR, multitarget TKIs, CTLA-4 inhibitors, and transarterial radioembolization, can produce a synergic effect to achieve antitumor activity as compared to PD-1/PD-L1 inhibitor monotherapy [20, 92, 94, 102]. Fifth, only a combination therapy of PD-1/PD-L1 inhibitors and VEGFR-TKIs was analyzed in a previous meta-analysis [118]. By comparison, PD-1/PD-L1 inhibitors combined with VEGFR-TKIs, multitarget TKIs, or CTLA-4 inhibitors were analyzed in our present meta-analysis. We further found that PD-1/PD-L1 inhibitors combined with multitarget TKIs may have a better antitumor effect on advanced HCC than PD-1/PD-L1 inhibitors combined with VEGFR-TKIs or CTLA-4 inhibitors. Sixth, only a few AEs, such as fatigue, rash, pruritus, and increased AST level, were described in two previous meta-analyses [117, 118]. By comparison, all AEs were reviewed, and the most common AEs, including hypertension, hand-foot syndrome, fatigue, proteinuria, and RCCEP, were quantitatively analyzed in our meta-analysis. Lastly, in a previous meta-analysis, patients receiving PD-1/PD-L1 inhibitor combination therapy might have a lower probability of drug withdrawal due to AEs than those receiving PD-1/PD-L1 inhibitor monotherapy [118]. However, on the basis of the data from a larger number of patients and PD-1/PD-L1 inhibitors included, we found a similar probability of drug withdrawal between the two groups.

Of course, our meta-analysis had several limitations. First, most of the included studies were single-arm studies, suggesting that the quality of evidence is relatively poor. Second, the dosage of PD-1/PD-L1 inhibitors was heterogeneous among the included studies, which compromises further subgroup analyses. Third, the characteristics of the study population, such as Child–Pugh class and Eastern Cooperative Oncology Group performance status, may influence the efficacy and safety of PD-1/PD-L1 inhibitors for advanced HCC, but cannot be sufficiently extracted, which fails to perform further subgroup analysis. Fourth, because the use of PD-1/PD-L1 inhibitors was the major intervention evaluated in our study, the type of TKIs combined was not specified. However, it should be noted that TKIs differed vastly in terms of their targets and efficacy.

CONCLUSION

PD-1/PD-L1 inhibitors increase tumor response and prolong survival of patients with advanced HCC as compared to multitarget TKIs. Additionally, PD-1/PD-L1 inhibitor combination therapy should be superior to PD-1/PD-L1 inhibitor monotherapy in terms of efficacy. Therefore, PD-1/PD-L1 inhibitor monotherapy and combination therapy should be considered as the first-line option for the treatment of advanced HCC. Certainly, more high-quality prospective studies are needed to validate these findings in future.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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