

Efficacy of immune checkpoint inhibitor as maintenance therapy for advanced or metastatic cancers

A meta-analysis of randomized controlled trials

Dun-Chang Mo, MD^{a,*} , Jian-Feng Huang, MD^a, Peng-Hui Luo, MD^a, Shang-Xiao Huang, MD^a, Han-Lei Wang, MD^a

Abstract

Background: This study aimed to evaluate the efficacy of immune checkpoint inhibitors (ICIs) as maintenance therapy for advanced or metastatic cancers.

Methods: The PubMed, Embase, and Cochrane Library databases were searched for eligible randomized controlled trials. A meta-analysis of eligible studies investigating the outcomes including progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) with a significance level set to 0.05 was performed.

Results: Five RCTs (n = 2828) were identified in this analysis. The pooled hazard ratios (HRs) of PFS and OS for ICI maintenance therapy were 0.88 (95% CI: 0.68–1.13, P = .31) and 0.82 (95% confidence interval [CI]: 0.74–0.92, P = .0005), respectively; the pooled odds ratio (OR) of ORR was 2.24 (95% CI: 1.23–4.09, P = .0008). Subgroup analysis indicated that anti-PD-L1 antibody significantly improved the OS (P = .0008), while anti-PD-1 and anti-PD-1 plus anti-cytotoxic T lymphocyte antigen 4 antibodies significantly prolonged the PFS of patients.

Conclusion: ICI maintenance therapy enhanced the survival of patients with advanced or metastatic cancers.

Abbreviations: CTLA-4 = cytotoxic T lymphocyte antigen 4, HR = hazard ratio, ICI = immune checkpoint inhibitor, OR = odds ratio, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death protein-1, PD-L1 = programmed cell death 1 ligand 1, PFS = progression-free survival, RCT = randomized controlled trial.

Keywords: efficacy, immune checkpoint inhibitor, maintenance therapy, meta-analysis, PD-1/PD-L1/CTLA-4

1. Introduction

Patients with advanced-stage or metastatic cancers have limited treatment options and a relatively poor prognosis; hence, maintenance therapy is a very important treatment strategy for these patients.^[1,2] The basic principle of maintenance therapy is based on the assumption that residual tumors contain clones that are still sensitive to one or more drugs used in combined induction therapy, so it can prolong tumor control and reduce the side effects.^[3] This means that the possibility of maintaining the effect is essentially random, except for drugs targeting the tumor cells or microenvironment. Although most patients with advanced-stage or metastatic cancers may respond to previous systemic therapies, the responses are not durable, and maintenance therapy is required to reduce the risk of disease progression and deaths.^[4,5] Maintenance treatment options, such as chemotherapy, endocrine therapy, targeted agent, and

tumor vaccine, are effective for various malignant tumors,^[6–9] among which systemic chemotherapy is the most commonly used treatment strategy in the clinical setting. However, the overall treatment effect for most tumors is not ideal, and the severe toxicities of chemotherapy usually cause significant harm to patients.^[2] Therefore, new maintenance therapies are warranted to improve the survival of advanced-stage or metastatic cancer patients.

In recent years, immune checkpoint inhibitors (ICIs), including anti-programmed cell death 1 ligand 1 (PD-L1)/anti-programmed cell death 1 (PD-1) and anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibodies have changed the treatment landscape for cancer patients.^[10–12] Either single-agent ICI, double-agent ICIs, or ICI combined with other systemic therapies has shown promising anti-tumor activity in advanced-stage or metastatic solid cancers.^[13–15] Moreover, previous clinical trials demonstrated that adjuvant/neoadjuvant therapy with ICIs

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Ethical approval is not required since this analysis is based on published research. PROSPERO registration number: CRD42022312031.

^a Radiotherapy Department, The Third Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.

*Correspondence: Dun-Chang Mo, Radiotherapy Department, The Third Affiliated Hospital of Guangxi Medical University, Dan-Cun Road No. 13, Nanning, Guangxi, China (e-mail: modunchang2018@163.com).

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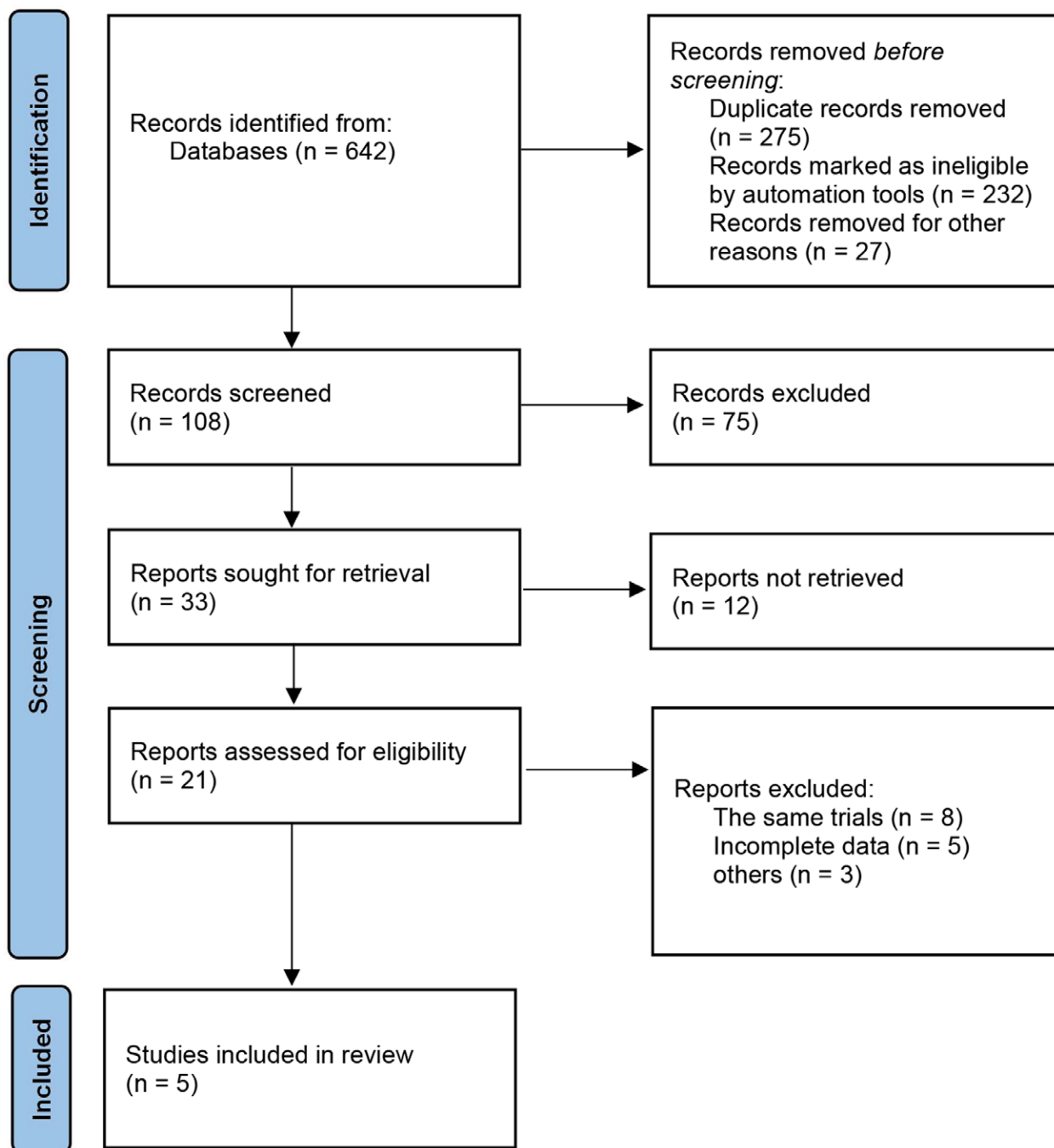


Figure 1. Flow chart of the selection process.

could also benefit patients with early-stage to middle-stage tumors.^[16,17] However, despite great progress, whether ICI maintenance therapy prolongs the survival of patients with advanced-stage or metastatic cancers remains unclear, and guidelines for ICI maintenance treatment in various types of cancers have not yet been established. Thus, this meta-analysis of current RCTs aimed to evaluate the efficacy of ICI maintenance therapy in advanced-stage or metastatic solid cancers.

2. Materials and Methods

2.1. Search strategy and selection criteria

We searched the PubMed, Embase, and Cochrane Library databases from inception until March 2022 for eligible trials. Clinical

studies were identified using the following terms: “PD-1, PD-L1, CTLA-4, immune checkpoint inhibitor, immune checkpoint blockade, immunotherapy, pembrolizumab, nivolumab, ipilimumab, atezolizumab, tremelimumab, avelumab, durvalumab, spartalizumab, toripalimab, tislelizumab, camrelizumab, maintenance, and randomized controlled trials.” The reference lists of all relevant studies were manually checked to identify additional articles. Studies that included patients diagnosed with advanced-stage or metastatic solid cancers through pathological and imaging examinations; studies that used ICIs as maintenance therapy; studies that compared the efficacy of placebo, observation, or other systemic therapies, such as chemotherapy, target therapy, and endocrine therapy; studies whose outcomes included objective response rate (ORR), progression-free survival (PFS), and/or overall survival (OS); and randomized controlled trials (RCTs)

were included in the analysis. Meanwhile, non-English articles; non-RCTs, reviews, meta-analysis, letters, or case reports; and basic experiments or animal studies were excluded. The trials identified during the search were independently screened for inclusion by 2 authors (M.D.C. and H.J.F.). Any disagreements were arbitrated by a third author (L.P.H.).

2.2. Data extraction and quality assessment

Two authors (H.J.F. and L.P.H.) independently reviewed the following data extracted from the selected literatures: author details, the trial name, publication year, tumor stage, age, sex, sample size, and interventions. The hazard ratios (HRs) with the corresponding 95% confidence interval (CIs) for analysis of PFS and OS, and the odds ratios (ORs) with the corresponding 95% CIs for analysis of ORR were extracted from the eligible trials. Data on the PFS and OS of patients with PD-L1-positive (tumor proportion score of ≥1%) and PD-L1-negative (tumor proportion score of < 1%) tumors were also extracted if available. Any discrepancy was resolved by discussion and consensus. Two authors (W.H.L. and H.S.X.) independently assessed the methodological quality of the included RCTs using the Cochrane Collaboration’s tool.^[18]

2.3. Statistical analysis

Meta-analysis was performed using Review Manager (version 5.4, The Cochrane Collaboration, Copenhagen). The OS and PFS were pooled as HR with the corresponding 95% CI, while the ORR was pooled as OR with the corresponding 95% CI. Heterogeneity between studies was assessed using the Cochran Q test and I² tests in the meta-analysis. A random effects model was used when the heterogeneity was considered high (I² ≥ 50%, P < .1). If the heterogeneity was considered low (I² ≤ 50%, P > .1), a fixed effects model was applied. A P value of <.05 was considered significant.

3. Results

3.1. Search results and study characteristics

We identified 642 literatures, of which 5 eligible RCTs including 2828 patients were selected according to the inclusion criteria^[19–23] (Fig. 1). Among the 5 independent RCTs, all patients were diagnosed with advanced-stage or metastatic solid cancers by pathological and imaging examinations, and received ICIs as maintenance therapy after receiving systemic therapies. All articles were published between 2020 and 2021. The ICIs used in the experimental arm of these RCTs included one anti-CTLA-4 antibody (ipilimumab), 2 anti-PD-1 antibodies (nivolumab and pembrolizumab), and 2 anti-PD-L1 antibodies (avelumab and durvalumab). The control arms in 4 RCTs^[19,20,22,23] were similar (best supportive care, placebo or observation), and only 1 RCT^[21] used chemotherapy as a control treatment. The characteristics of the selected trials are shown in Table 1.

3.2. Influence of ICI maintenance therapy on PFS

All RCTs reported the PFS with 7 comparisons. The meta-analysis indicated that ICI maintenance therapy did not lead to a significant improvement in PFS (HR = 0.88, 95% CI: 0.68–1.13, P = .31). Results of the meta-analysis are shown in Figure 2. Subgroup analysis showed that both anti-PD-1 and anti-PD-1 plus anti-CTLA-4 antibodies were associated with significantly improved PFS (HR = 0.67, 95% CI: 0.56–0.79, P < .00001 and HR = 0.72, 95% CI: 0.60–0.87, P = .00006, respectively). However, among patients treated with anti-PD-L1 antibody, none showed improvement in PFS (HR = 1.08, 95% CI: 0.68–1.71, P = .74).

Only 2 articles reported the complete data of PFS according to the PD-L1 expression levels.^[19,21] The meta-analysis showed that anti-PD-L1 antibodies (avelumab and durvalumab) as maintenance therapy significantly improved the PFS (HR = 0.58, 95% CI: 0.45–0.75, P < .0001) of patients with PD-L1-positive

Table 1
Characteristic of included randomized controlled trials.

Study	Tumor	Phase	Stage	Sample size		Age, median (range)	Male, n (%)	Previous treatment	Maintenance therapy
				Arms	N				
Powles 2020 ^[19] (JAVELIN Bladder 100)	Urothelial cancer	3	Advanced or metastatic	Study	350	68 (37–90)	NA	Chemotherapy	Avelumab (10 mg/kg) intravenously every 2 wk
				Control	350	69 (32–89)	NA	Chemotherapy	Best supportive care
Monk 2021 ^[20] (JAVELIN Ovarian 100)	Epithelial ovarian cancer	3	Advanced	Study (arm a)	322	59 (52–67)	NA	Chemotherapy	Avelumab (10 mg/kg) intravenously every 2 wk
				Study (arm b)	331	60 (50–66)	NA	Chemotherapy plus avelumab	Avelumab (10 mg/kg) intravenously every 2 wk
				Control	335	57 (49–66)	NA	Chemotherapy	Observation
				Control	335	57 (49–66)	NA	Chemotherapy or chemotherapy plus avelumab	Observation
Bachelot 2021 ^[21] (SAFIRO2-BREAST IMMUNO)	Breast cancer	2	Metastatic	Study	131	NA	NA	Chemotherapy	Durvalumab (10 mg/kg) intravenously every 2 wk
Owonikoko 2021 ^[22] (CheckMate 451)	Small-cell lung cancer	3	Extensive disease	Study (arm a)	279	64 (39–85)	180 (65)	Chemotherapy	Nivolumab 1 mg/kg plus ipilimumab 3mg/kg once every 3 wk for 12 wk followed by nivolumab 240 mg once every 2 wk
				Study (arm b)	280	65 (32–84)	177 (63)	Chemotherapy	Nivolumab 240 mg once every 2 wk
				Control	275	64 (44–84)	175 (64)	Chemotherapy	Placebo
Galsky 2020 ^[23] (HCRN GU14-182)	Urothelial cancer	2	Metastatic	Study	55	68 (41–83)	39 (71)	Chemotherapy	Pembrolizumab 200 mg intravenously once every 3 wk
				Control	52	65 (44–87)	42 (81)	Chemotherapy	Placebo

NA = not available.

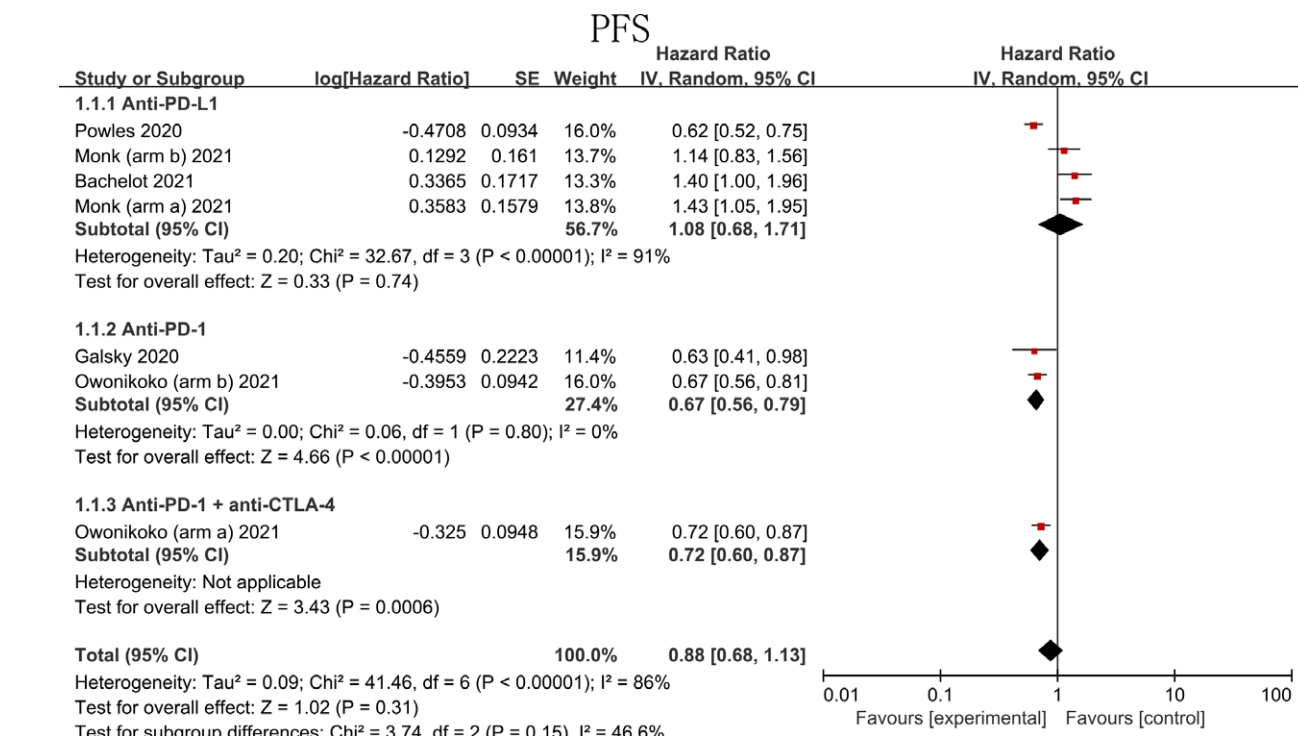


Figure 2. Analysis of PFS. PFS = progression-free survival.

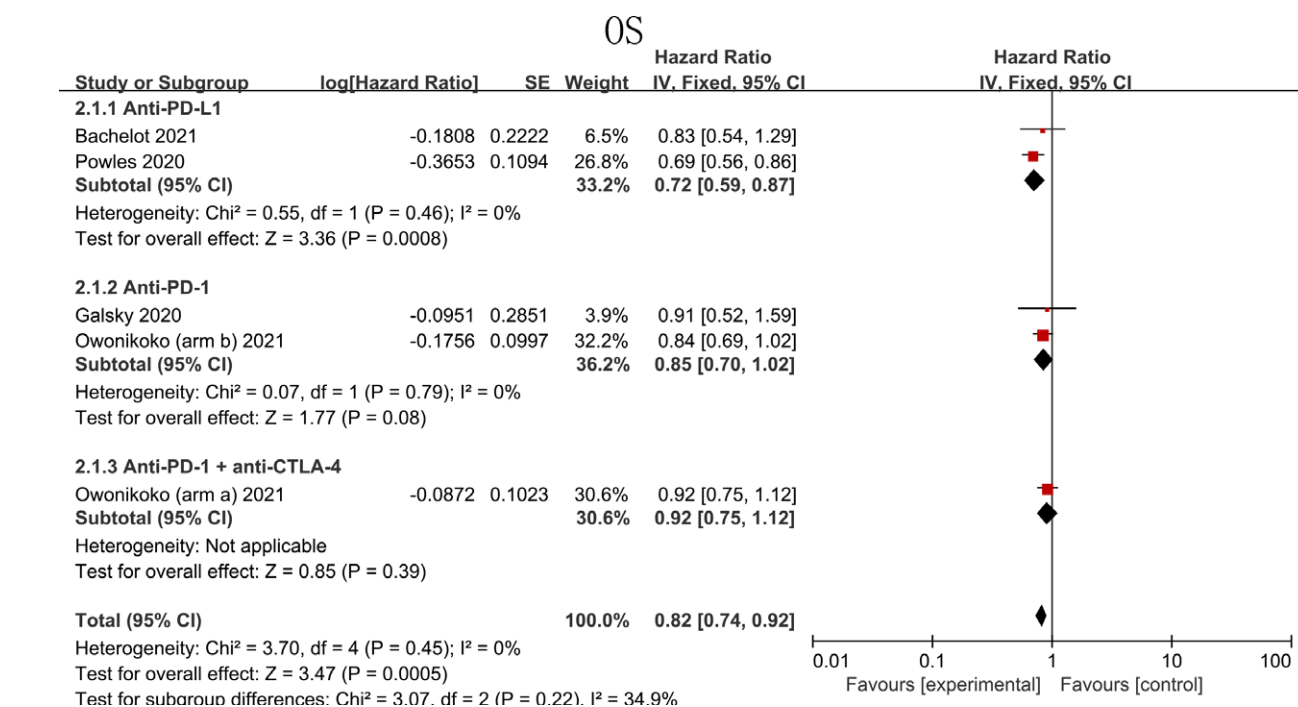


Figure 3. Analysis of OS. OS = overall survival.

tumors. However, the PFS did not improve (HR = 1.08, 95% CI: 0.36–3.20, P = .89) in patients with PD-L1-negative tumors (Fig. 3).

3.3. Influences of ICI maintenance therapy on OS

Data of OS were reported in 4 of 5 RCTs with 5 comparisons. As shown in Figure 4, the meta-analysis indicated that the OS of

the patients receiving ICI maintenance therapy was much higher than that of patients receiving the control treatment (HR = 0.82, 95% CI: 0.74–0.92, P = .0005). Subgroup analysis showed that anti-PD-L1 antibody was associated with significantly improved OS (HR = 0.72, 95% CI: 0.59–0.87, P = .0008), while the OS did not improve in patients treated with anti-PD-1 (HR = 0.85, 95% CI: 0.70–1.02, P = .08) and anti-PD-1 plus anti-CTLA-4 antibodies (HR = 0.92, 95% CI: 0.75–1.12, P = .39).

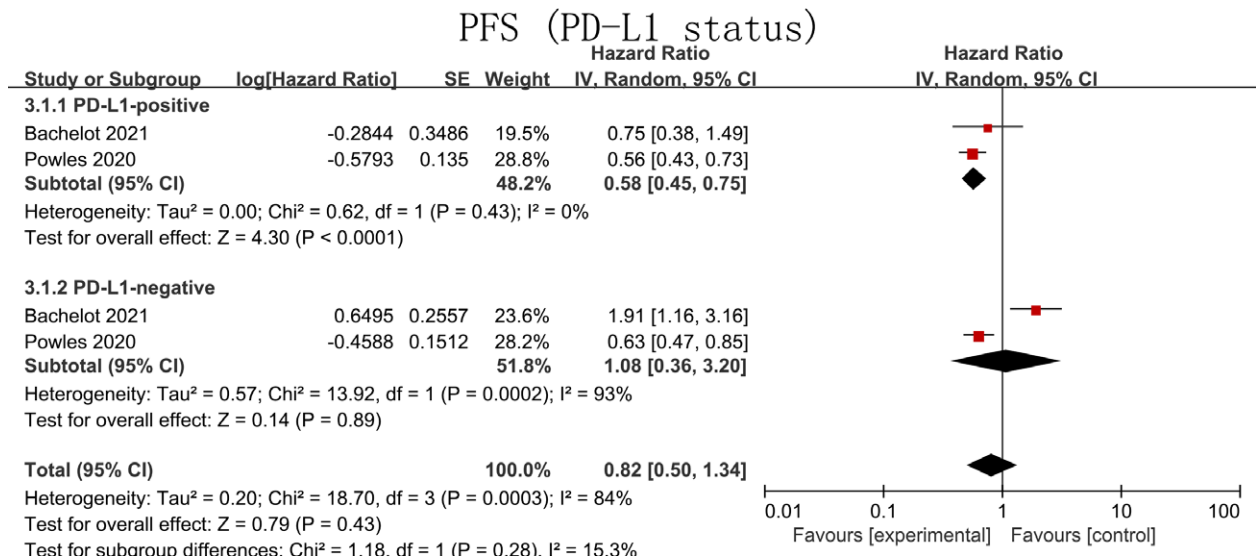


Figure 4. Subgroup analysis of the PFS according to the PD-L1 expression level. PD-L1 = programmed cell death 1 ligand 1, PFS = progression-free survival.

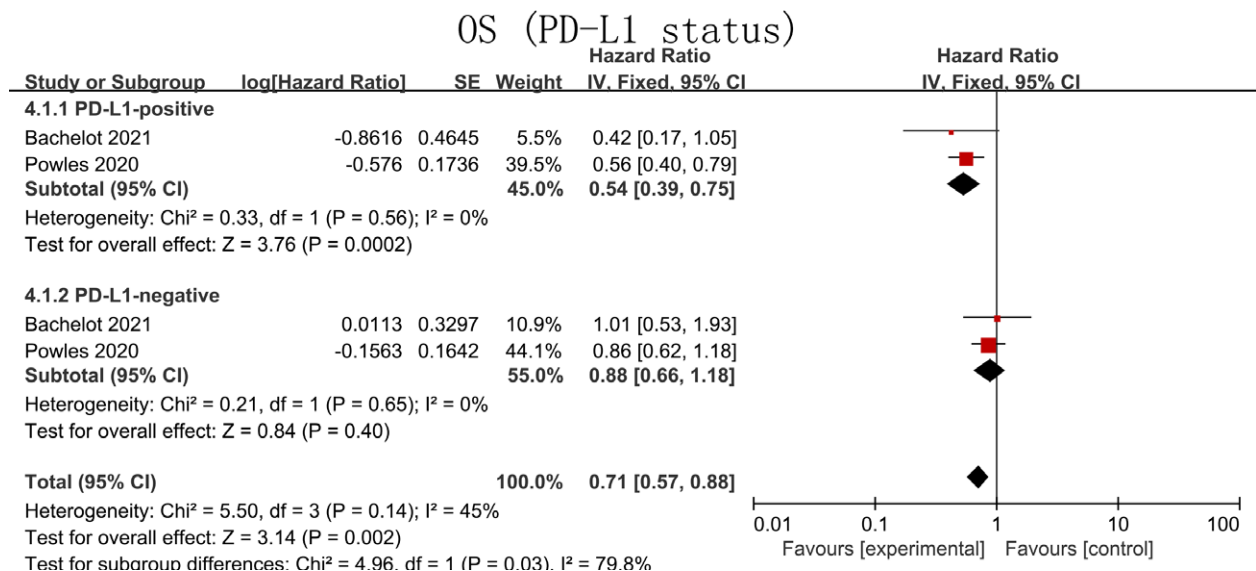


Figure 5. Subgroup analysis of the OS according to the PD-L1 expression level. OS = overall survival, PD-L1 = programmed cell death 1 ligand 1.

The OS data according to the PD-L1 expression levels were extracted from 2 trials.^[19,21] As shown in Figure 5, patients with PD-L1-positive tumors had significantly longer OS (HR = 0.54, 95% CI: 0.39–0.75, *P* = .0002), while those with PD-L1-negative tumors showed no OS improvement (HR = 0.88, 95% CI: 0.66–1.04, *P* = .40).

3.4. Influence of ICI maintenance therapy on ORR

In the meta-analysis of ORR, the outcome indicated that ICI maintenance therapy greatly enhanced the ORR of patients compared with control treatment (OR = 2.24, 95% CI: 1.23–4.09, *P* = .0008) (Fig. 6). The subgroup analysis indicated that both anti-PD-1 and anti-PD-1 plus anti-CTLA-4 antibodies were associated with significantly higher ORR (OR = 3.22, 95% CI: 1.83–5.67, *P* < .0001 and OR = 2.28, 95% CI: 1.09–4.76, *P* = .03). However, no ORR improvement (OR = 1.84, 95% CI: 0.66–5.15, *P* = .25) was observed in patients treated with anti-PD-L1 antibody.

3.5. Quality of included studies

The results of the quality assessment of all RCTs are presented in Figure 7. Results showed that the included trials were of high quality.

4. Discussion

Immunotherapy with ICI plays an important role in the treatment of various cancer types, and ICI treatment has changed the outcomes of advanced-stage or metastatic solid cancers.^[10–12] Although existing evidence had shown that ICI or their combination therapies demonstrated promising efficacy in patients with advanced-stage or metastatic solid cancers,^[24–26] current research findings of ICI maintenance treatment remain inconsistent. Galsky et al^[23] reported that maintenance pembrolizumab prolonged the PFS (HR = 0.65, 95% CI: 0.49–0.86) in patients with metastatic urothelial cancer who achieved at least stable disease following first-line platinum-based chemotherapy. A international multi-center phase 3 JAVELIN

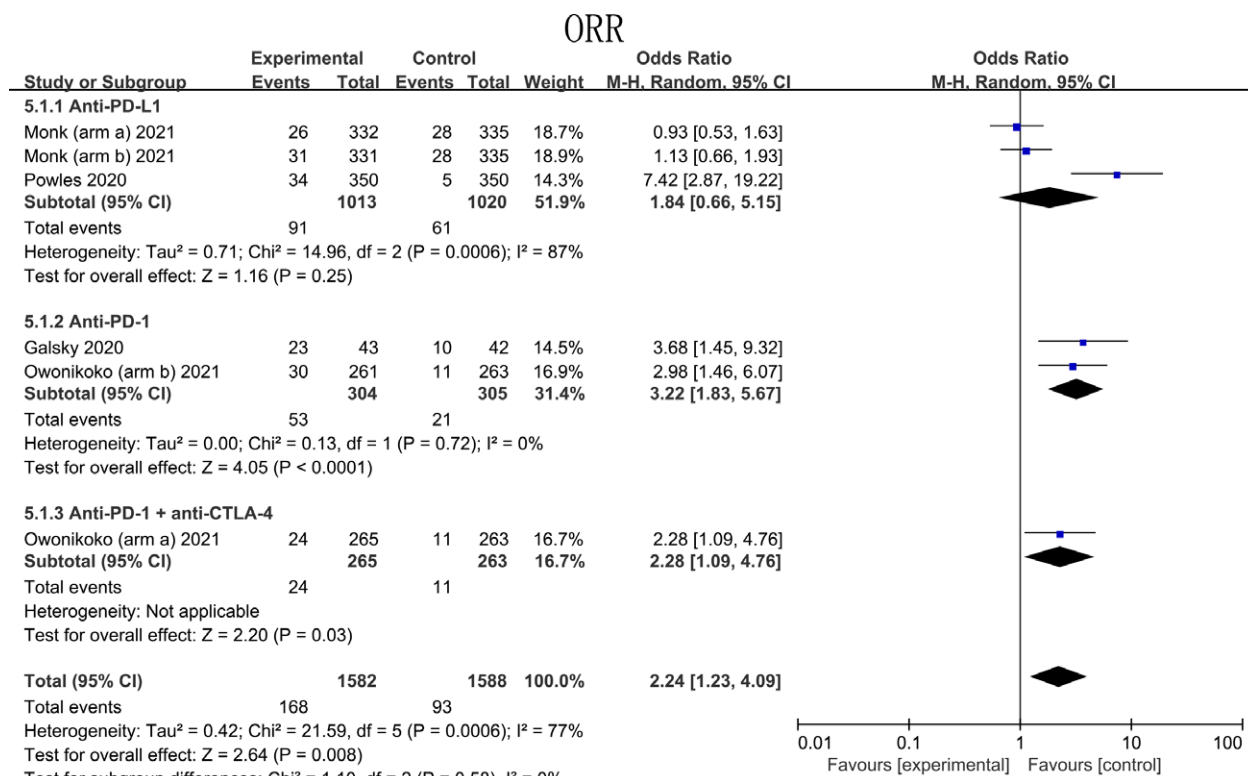


Figure 6. Analysis of ORR. ORR = objective response rate.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bachelot 2021	+	?	?	?	+	+	+
Galsky 2020	+	?	+	+	+	+	+
Monk 2021	+	?	?	?	+	+	+
Owonikoko 2021	+	?	+	+	+	+	?
Powles 2020	+	+	+	?	+	+	+

Figure 7. Evaluation of the quality of all included articles.

Ovarian 100 trial^[20] reported that avelumab maintenance therapy was not associated with longer PFS (HR = 1.43, 95% CI: 1.05–1.95) compared with observation in advanced epithelial ovarian cancer patients. In the phase 2 SAFIR02-BREAST IMMUNO trial,^[21] maintenance therapy with durvalumab did not improve the PFS (HR = 1.04, 95% CI: 1.00–1.96) and OS (HR = 0.84, 95% CI: 0.54–1.29) in patients with metastatic breast cancer. Thus, whether ICIs could be used as maintenance therapy for cancer patients and worth clinical promotion remains controversial.

To our knowledge, this meta-analysis was the first to directly compare the efficacy of ICI maintenance therapy with that of traditional treatments (placebo, observation, or chemotherapy) in advanced or metastatic cancers. Results showed that ICI maintenance therapy was associated with significantly improved OS and ORR compared with the control treatment, which indicated that ICI as maintenance therapy may have a great clinical value for the treatment of advanced-stage or metastatic solid cancers. Similar results were found by other clinical trials. The phase 3 PACIFIC trial^[27,28] reported that durvalumab after chemoradiotherapy resulted in significantly prolonged PFS (HR = 0.52, 95% CI: 0.42–0.65) and OS (HR = 0.72, 95% CI: 0.59–0.89) compared with placebo in patients with stage III unresectable non-small-cell lung cancer who did not experience disease progression after concurrent therapy. In the KEYNOTE-564 trial,^[29] pembrolizumab significantly improved the disease-free survival (HR = 0.68, 95% CI: 0.53–0.87) compared with placebo after surgery in patients with kidney cancer who had high risk of recurrence. These results suggest that ICI as maintenance or sequential treatment demonstrates great clinical efficacy for cancer patients who achieved disease control after receiving previous treatments.

Despite the improvement in OS and ORR, this meta-analysis showed that ICI maintenance therapy did not lead to a significant difference in PFS (HR = 0.88, 95% CI: 0.68–1.13, P = .31). Subgroup analysis showed that both anti-PD-1 and anti-PD-1 plus anti-CTLA-4 antibodies were associated with significantly

improved PFS and ORR. However, patients treated with anti-PD-L1 antibody did not show better ORR and PFS. Surprisingly, the subgroup analysis of OS showed opposite results. Patients who received anti-PD-1 (HR = 0.85, 95% CI: 0.70–1.02, $P = .08$) and anti-PD-1 plus anti-CTLA-4 antibodies (HR = 0.92, 95% CI: 0.75–1.12, $P = .39$) did not show an OS benefit, but longer OS was observed in those treated with anti-PD-L1 antibody. These results also support the benefit of ICI maintenance therapy in patients with advanced-stage or metastatic solid cancers, although only PD-L1 antibody achieved a significant OS difference. In 2019, a study by Rowinski et al^[4] reported that although maintenance strategies such as chemotherapy, targeted therapy, and immunotherapy were proven effective, the duration of treatments remained elusive. In this study, the duration of ICI maintenance therapies remained inconsistent, which possibly caused an impact on the outcomes of patients. In addition, the PD-L1 expression level was a valuable biomarker for predicting the outcomes of cancer patients who received ICI monotherapies.^[30,31] However, evidence showed that PD-L1 had little value in predicting the outcomes for patients who received ICI combination therapies.^[32,33] In this study, longer PFS and OS were only observed among patients with PD-L1-positive tumors, suggesting that PD-L1 might be an independent prognostic factor for patients receiving anti-PD-L1 antibodies as maintenance therapy. However, as most current studies used single-agent ICI as maintenance therapy, the clinical value of PD-L1 as a biomarker for predicting the outcomes of ICI combination maintenance therapies needs further investigations.

This study has several shortcomings. First, only limited tumors (urothelial cancer, epithelial ovarian cancer, breast cancer, and small-cell lung cancer) and ICIs (1 CTLA-4 inhibitor [ipilimumab], 2 PD-1 inhibitors [nivolumab and pembrolizumab], and 2 PD-L1 inhibitors [avelumab and durvalumab]) were included in the analysis. Because the meta-analysis was performed in patients with different types of tumors and the antitumor mechanism of checkpoint inhibitors (including anti-PD-1/PD-L1 and anti-CTLA-4 antibodies) differed, thus causing heterogeneity. Second, the number of included RCTs is relatively small, and only 1 trial is included in the anti-PD-1 plus anti-CTLA4 agent group, which limited the evaluation of outcomes in this analysis. Third, age and gender were may influence the outcome assessment of patients. Owing to the insufficient data on age and gender, these factors were not analyzed. However, these 2 factors are considered significant and may be valuable for future studies. Finally, the follow-up time in some trials was not sufficiently long. The OS data were not reported in Monk et al's study,^[20] and the OS data were immature. Hence, a longer follow-up time is required.

5. Conclusion

The current meta-analysis demonstrated that ICIs as maintenance therapy improved the PFS or OS of patients with advanced-stage or metastatic cancers. However, this treatment was only beneficial among patients with PD-L1-positive tumors. PD-L1 might be used as a biomarker for predicting the outcome for patients receiving anti-PD-L1 antibodies as maintenance therapy. Due to the limitations of this study, further investigations are required to provide more evidence.

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Author contributions

M.D.C. and H.J.F. contributed to the study design and writing. H.J.F. and L.P.H. performed the data collection and selection.

H.S.X. and W.H.L. performed the data analysis. All authors read and approved the final manuscript.

Conceptualization: Dun-Chang Mo.

Data curation: Jian-Feng Huang, Peng-Hui Luo, Shang-Xiao Huang.

Software: Peng-Hui Luo, Shang-Xiao Huang, Han-Lei Wang.

Writing – original draft: Dun-Chang Mo.

Writing – review & editing: Dun-Chang Mo, Jian-Feng Huang, Peng-Hui Luo, Shang-Xiao Huang, Han-Lei Wang.

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