Efficacy and safety of adjuvant therapy with PD-1/PD-L1 inhibitors in cancer

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Abstract. Anti-programmed cell death protein-1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) antibodies have been widely used in cancers. The present study aimed to evaluate the efficacy and safety of PD-1/PD-L1 inhibitors in human cancers. Studies were searched from Cochrane Library, PubMed and Embase databases. Randomized controlled trials (RCTs) that investigated adjuvant therapy with anti-PD-1/PD-L1 agents in solid cancers were eligible for inclusion. As the primary focus of the meta-analysis, clinical outcome measures including overall survival (OS), disease-free survival (DFS), and adverse events (AEs) were analyzed by Stata 15.0 software. A total of six RCTs (n=4,436) met the inclusion criteria. The DFS [hazard ratio (HR)=0.71; 95% confidence interval (CI): 0.63-0.78; P<0.001] and OS (HR=0.66, 95% CI: 0.46-0.86, P<0.001) of patients were significantly prolonged by adjuvant immunotherapy. Subgroup analysis indicated that significantly improved DFS was observed in patients treated with different anti-PD-1/PD-L1 drugs (nivolumab, pembrolizumab, or atezolizumab), as well as in those with different tumors (melanoma, urothelial carcinoma, esophageal or gastroesophageal junction cancer, or renal cell carcinoma), and PD-L1 status [negative (<1%) or positive (≥1%)]. However, PD-1/PD-L1 inhibitors was associated with increased ≥ grade 3 treatment-related AEs (odds ratio=1.63; 95% CI: 1.20-2.21; P=0.002). The available evidence suggests that adjuvant therapy with PD-1/PD-L1 inhibitors provided more survival benefit than placebo for patients with cancer, with increased grade 3 or higher AEs. Prospero registration no. CRD42021290654.

Introduction

Surgery is the standard treatment for most early to intermediate stages of solid cancers (1). The surgical excision of the primary tumor, along with adjuvant therapy, reduces the risk of disease recurrence and distant metastasis for cancers (2,3). Adjuvant treatment options, including chemotherapy, radiotherapy, and endocrine therapy (4-6), have been widely used in resected cancers for several decades. Targeted agents such as imatinib (7) and osimertinib (8) are also found to significantly improve the survival of patients with high-risk primary gastrointestinal stromal tumor and EGFR mutation-positive non-small-cell lung cancer, respectively. However, despite the advent of adjuvant therapies, the severe toxicities of chemotherapy usually cause significant pain to patients with cancer. Although some patients can benefit from adjuvant treatment with targeted agents, this type of treatment is only for patients with specific and sensitive gene mutations, which occur in a small number of patients. In addition, due to the drug resistance of tumors, disease recurrence and distant metastasis are also unavoidable problems (9). Therefore, more effective and safer adjuvant treatment strategies are needed to improve survival for patients with cancer.

In recent years, adjuvant immunotherapy with anti-programmed cell death protein-1 (anti-PD-1)/programmed cell death 1 ligand 1 (PD-L1) antibodies, such as pembrolizumab (a humanized IgG4 monoclonal anti-PD-1 antibody), nivolumab (a fully human IgG4 anti-PD-1 antibody), and atezolizumab (MPDL3280A, an IgG anti-PD-L1 antibody), has shown promising anti-tumor activity and safety in various solid cancers (10-12). Eggermont *et al* (13) report that adjuvant pembrolizumab significantly improves recurrence-free survival for patients with completely resected high-risk stage III melanoma. The one-year recurrence-free survival was 75.4% for pembrolizumab vs. 61.0% for placebo [hazard ratio (HR)=0.57; 98.4% confidence interval (CI): 0.43-0.74; P<0.001]. In the CheckMate 238 trial (11), adjuvant nivolumab

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resulted in significantly prolonged recurrence-free survival and a lower rate of grade 3 or higher adverse events (AEs) than ipilimumab among patients with resected stage IIIB-IV melanoma. In the KEYNOTE-564 trial (14), adjuvant treatment with pembrolizumab was associated with a significantly longer disease-free survival (DFS) compared with placebo after nephrectomy among patients with renal cell carcinoma who were at high risk for recurrence. In the CheckMate 274 trial (15) and IMMUNED trial (16), DFS was longer with adjuvant nivolumab than with placebo in patients with high-risk muscle-invasive urothelial carcinoma. In the CheckMate 577 trial (17), nivolumab adjuvant therapy showed a significantly longer DFS than placebo in patients with resected esophageal or gastroesophageal junction cancer who received neoadjuvant chemoradiotherapy in previous treatments.

Clinical trials (13-18) have shown that adjuvant therapy with PD-1/PD-L1 inhibitors has promising efficacy and safety in solid cancers and this type of treatment strategy may become a new standard of care for malignant tumors. However, despite encouraging results, current treatment guidance for adjuvant therapy with PD-1/PD-L1 inhibitors in solid cancers is lacking. Therefore, a meta-analysis is warranted to present evidence regarding the clinical efficacy and safety of adjuvant therapy with PD-1/PD-L1 inhibitors in solid cancers.

Materials and methods

Strategy of study screening. Potentially relevant studies were obtained by searching the databases of PubMed, Embase, and Cochrane Library from inception until April 2022. For the literature search, the present study used any of the following key words: 'Immune checkpoint blockade, immune checkpoint inhibitor, immune therapy, immunotherapy, PD-1, PD-L1, pembrolizumab, nivolumab, atezolizumab, tremelimumab, avelumab, durvalumab, adjuvant, postoperative and randomized controlled trial'. It also manually searched relevant references to identify other relevant clinical trials. The inclusion criteria were as follows: i) Participants-patients diagnosed as cancers by post-operative pathology; ii) intervention-adjuvant therapy with PD-1/PD-L1 inhibitors; iii) comparison-placebo, observation, or other adjuvant treatments, such as chemotherapy, target therapy, and endocrine therapy; iv) outcomes-reporting data of DFS, overall survival (OS), and grade 3 or higher AEs; v) randomized controlled trials (RCTs). The exclusion criteria were as follows: i) Non-English articles; ii) non-RCTs, reviews, meta-analysis, letters, or case reports; and iii) animal studies or basic experiments. The trials identified via the search were independently screened for inclusion by two authors; MDC and LZY. Any disagreements were arbitrated by a third author; CL.

Data extraction and quality assessment. The key information in the included articles was independently extracted by two reviewers; HJF and LPH. The key information included the study details, year, phase, tumors, sample size, age, sex, and regimens. Clinical outcomes including DFS, OS and grade 3 or higher treatment-related AEs were recorded for further analysis. The DFS data of patients with PD-L1-negative (<1%) and PD-L1-positive (≥1%) tumors were also recorded in detail. When multiple papers of the same trial were identified,
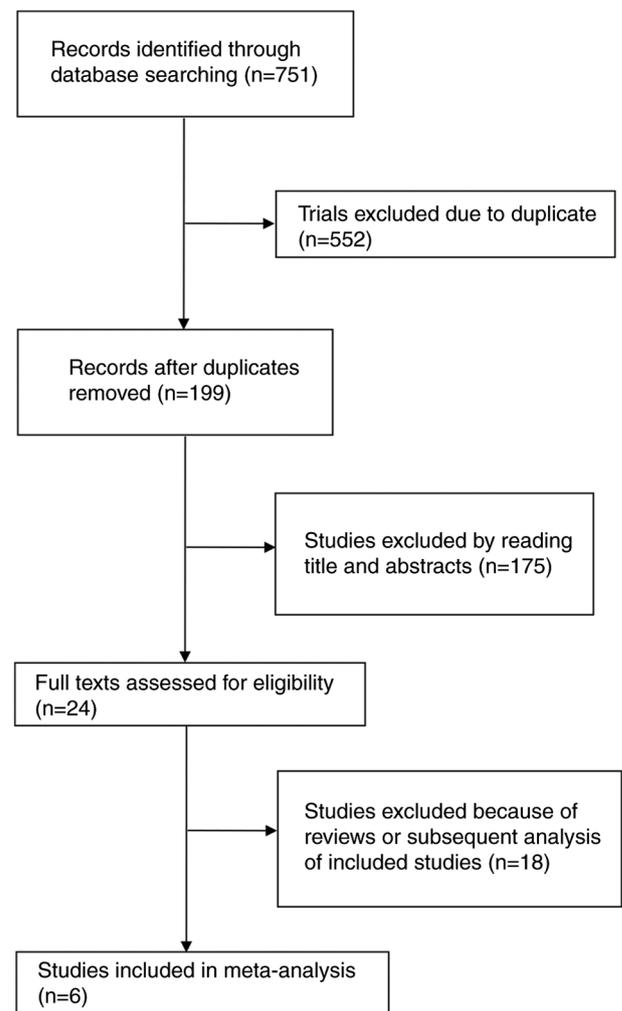

Figure 1. Flow diagram representing the selection process.

data were extracted and recorded as a single trial. If any discrepancy occurred, problems were resolved via discussions and consensus. Two authors; CL and WHL, used the Cochrane Collaboration risk of bias assessment tool to assess the risk of bias of the included RCTs (19).

Statistical analysis. The meta-analysis was conducted with Stata 15.0 software (Stata Corporation). HRs with 95% CIs were used to evaluate the influence of anti-PD-1/PD-L1 treatments on the DFS and OS of patients with cancer. Odds ratios (ORs) with 95% CI represented the effects of anti-PD-1/PD-L1 treatments on AEs. Between-study heterogeneity was analyzed using I-squared (I^2) tests in the meta-analysis. If the heterogeneity was considered high (either $I^2 > 50\%$ or $P < 0.1$), the randomized-effects model was applied; otherwise, the fixed-effects model was used. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Search results and study characteristics. Fig. 1 shows the flowchart of the selection process and detailed identification. After screening, six RCTs with a total of 4,436 patients were included (13-18). Among the six global, multi-center RCTs, five
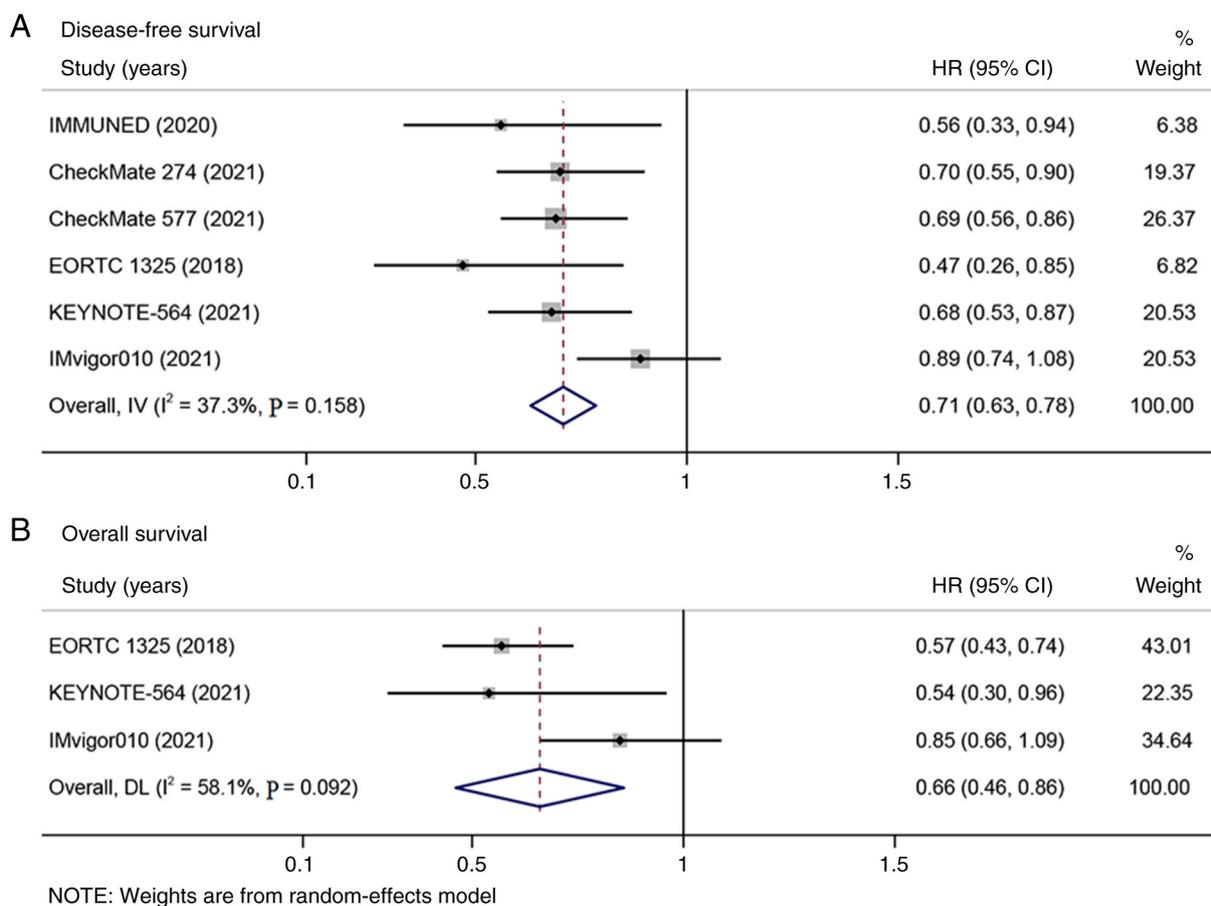
Figure 2. Meta-analysis for DFS and OS. Meta-analysis for (A) DFS and (B) OS. DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

were phase 3 studies (13-15,17,18), and the remaining study was a phase 2 study (16). All patients were diagnosed with solid cancers by post-operative pathology and received a PD-1/PD-L1 inhibitor in the adjuvant setting. Across these six trials, four types of malignancies were included: Melanoma, urothelial carcinoma, esophageal and gastroesophageal junction cancer, and renal cell carcinoma. All articles were published between 2018 and 2021. All anti-PD-1/PD-L1 agents were identified in the systematic evaluation, including three doses of nivolumab (15-17), two doses of pembrolizumab (13,14), and one dose of atezolizumab (18). Table I shows the main characteristics of the included studies.

Efficacy. DFS data were extracted from the six included studies and three publications reported the data of OS. In the DFS analysis, no heterogeneity was observed ($I^2 < 50\%$) (Fig. 2A). In the OS analysis, clear heterogeneity was observed ($I^2 > 50\%$; Fig. 2B). The meta-analysis indicated that adjuvant therapy with PD-1/PD-L1 inhibitors significantly improved DFS (HR=0.71; 95% CI: 0.63-0.78; P<0.001; Fig. 2A) and OS (HR=0.66; 95% CI: 0.46-0.86; P<0.001; Fig. 2B) compared with placebo or observation.

On the basis of the anti-PD-1/PD-L1 drugs (nivolumab, pembrolizumab, or atezolizumab), tumors (melanoma, urothelial carcinoma, esophageal or gastroesophageal junction cancer, or renal cell carcinoma), and PD-L1 status [negative (<1%) or positive (≥1%)], a subgroup analysis of DFS was performed. It was found that patients receiving adjuvant

therapy with PD-1/PD-L1 inhibitors was associated with significantly longer DFS than those receiving placebo in all subgroups (all P<0.001; Fig. 3A-C).

Safety. The rates of grade 3 or higher treatment-related AEs and immune-related AEs were extracted from five of the six included studies. Significant heterogeneity was found in the analysis of AEs ($I^2 > 50\%$; Fig. 4). The meta-analysis suggested that adjuvant therapy with PD-1/PD-L1 inhibitors cause more grade 3 or higher treatment-related AEs and immune-related AEs than placebo [OR=1.63; 95% CI: 1.20-2.21; and P=0.002 (Fig. 4A) and OR=5.86; 95% CI: 2.60-13.25; and P<0.001 (Fig. 4B), respectively].

Quality of the included studies. Fig. 5 shows the risks of bias of the included studies in this meta-analysis. The results demonstrated that the six eligible studies were of high quality and that the pooled analysis results were credible.

Discussion

Immune checkpoint inhibitors play an important role in the treatment of cancers (20) and anti-PD-1/PD-L1 treatments are widely used in advanced or metastatic cancers (21-23). However, the use of PD-1/PD-L1 inhibitors in the adjuvant setting for patients with cancer is still a tentative approach. Clinical trials show that adjuvant therapy with PD-1/PD-L1 inhibitors offers a better

Table I. The main characteristics of included studies.

Study (author, year)	Phase	Tumor	Sample size, n	Median age (years)	Male (%)	Regimens	Median DFS (months)	Grade 3 or higher immune-related AEs of Exp, %	(Refs.)
EORTC 1325 (Eggermont *et al* 2018)	3	Melanoma	Exp: 514; Con: 505	54 vs. 54	63 vs. 60	Pembrolizumab vs. placebo	NR vs. 20.0	7.1	(13)
KEYNOTE-564 (Choueiri *et al* 2021)	3	Renal-cell carcinoma	Exp: 496; Con: 498	60 vs. 60	70 vs. 72	Pembrolizumab vs. placebo	NR in both groups	18.9	(14)
CheckMate 274 (Bajorin *et al* 2021)	3	Urothelial carcinoma	Exp: 353; Con: 356	65 vs. 66	75 vs. 77	Nivolumab vs. placebo	22.9 vs. 13.7	17.9	(15)
IMMUNED (Zimmer *et al* 2020)	2	Melanoma	Exp: 59; Con: 52	57 vs. 59	53 vs. 63	Nivolumab vs. placebo	12.4 vs. 6.4	26.7	(16)
CheckMate 577 (Kelly *et al* 2021)	3	Esophageal or gastroesophageal junction cancer	Exp: 532; Con: 262	62 vs. 61	84 vs. 85	Nivolumab vs. placebo	22.4 vs. 11.0	13.3	(17)
IMvigor010 (Bellmunt *et al* 2021)	3	Urothelial carcinoma	Exp: 406; Con: 403	67 vs. 66	79 vs. 78	Atezolizumab vs. observation	19.4 vs. 16.6	16	(18)

Exp, experiment group; Con, control group; DFS, disease-free survival; AEs, adverse events; NR, not reached.
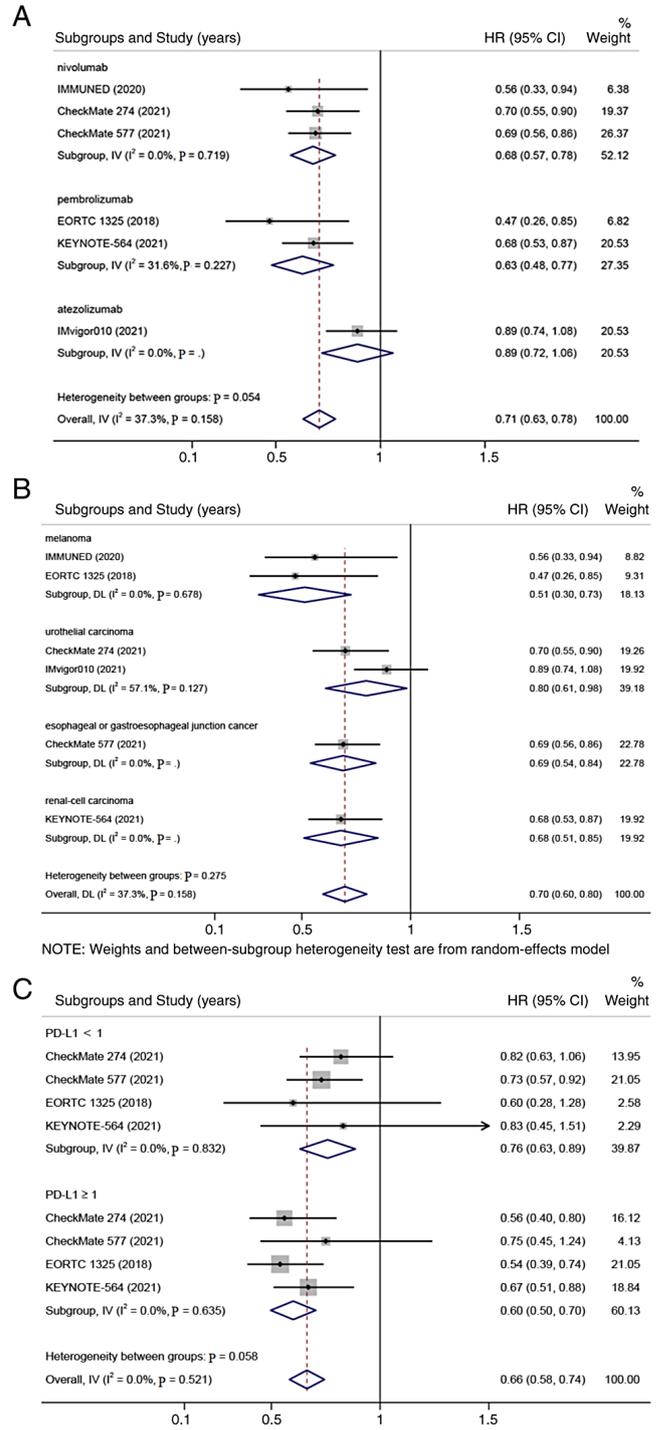

Figure 3. Subgroup analysis of DFS based on anti-PD-1/PD-L1 drugs, tumors, and PD-L1 status. Subgroup analysis of DFS based on (A) anti-PD-1/PD-L1 drugs (B) tumors and (C) PD-L1 status. DFS, disease-free survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death 1 ligand 1; HR, hazard ratio; CI, confidence interval.

survival benefit than placebo in various solid cancers (11,13-18). On the basis of the results of the CHECKMATE-238 and EORTC1325/KEYNOTE-054 trials, the US Food and Drug Administration approved PD-1 blocking agents nivolumab and pembrolizumab as adjuvant treatments for patients with high-risk melanoma (11,24). Although adjuvant therapy with PD-1/PD-L1 inhibitors has demonstrated promising efficacy in many resected solid cancers, a treatment guidance regarding
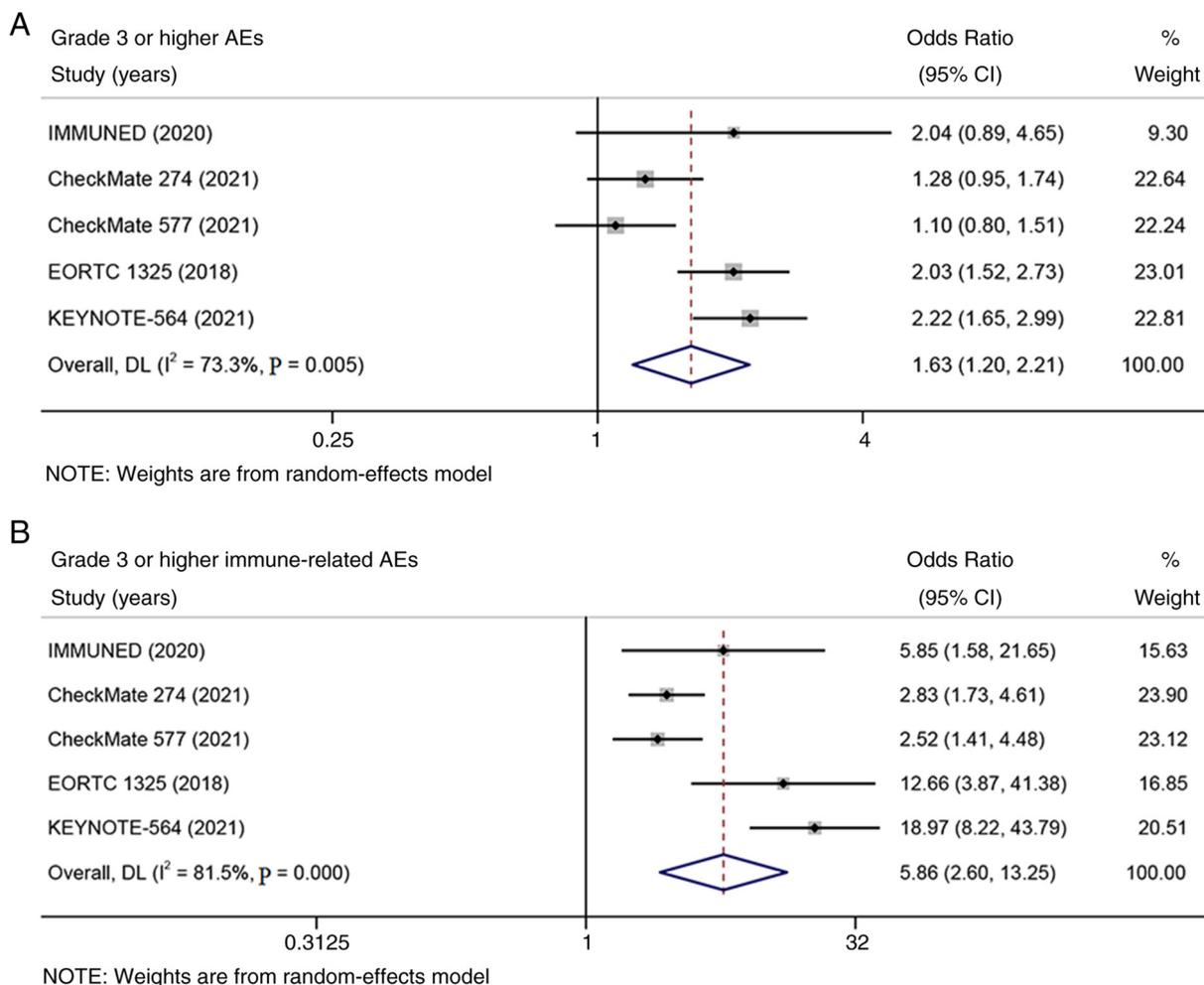
Figure 4. Meta-analysis for grade 3 or higher treatment-related AEs and immune-related AEs. (A) Grade 3 or higher treatment-related AEs and (B) grade 3 or higher immune-related AEs. AE, adverse event; CI, confidence interval.
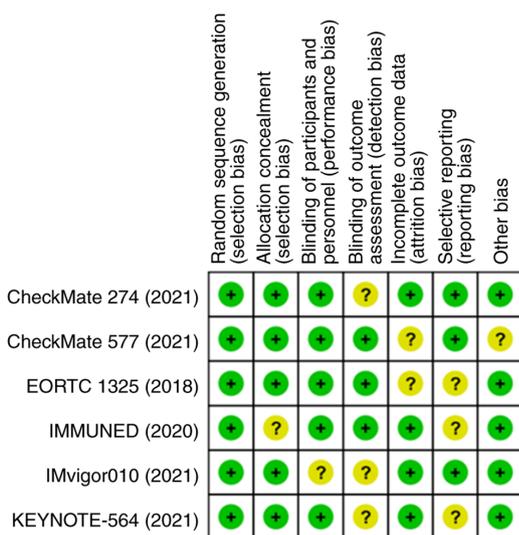

Figure 5. Quality evaluation of included studies.

The present meta-analysis showed that adjuvant therapy with PD-1/PD-L1 inhibitors significantly improved DFS (HR=0.71; 95% CI: 0.63-0.78; P<0.001) and OS (HR=0.66; 95% CI: 0.46-0.86; P<0.001) compared with placebo or observation in solid cancers, thus suggesting that adjuvant therapy with PD-1/PD-L1 inhibitors is more effective than placebo as adjuvant treatments for some types of solid cancers. Similar results were observed for adjuvant immunotherapy with ipilimumab, which is a cytotoxic T lymphocyte antigen 4 inhibitor. In the phase 3 EORTC 18071 trial (25), adjuvant ipilimumab resulted in a significantly longer recurrence-free survival than placebo (HR=0.75; 95% CI: 0.64-0.90; P=0.0013) for patients with completely resected high-risk stage III melanoma. In the IMMUNED trial (16), adjuvant therapy with nivolumab plus ipilimumab significantly improved recurrence-free survival compared with placebo (HR=0.23; 97.5% CI, 0.12-0.45; P<0.0001) in patients with stage IV melanoma with no evidence of disease. Moreover, the present analysis showed that significantly improved DFS was observed in subgroups including anti-PD-1/PD-L1 drugs (nivolumab, pembrolizumab, or atezolizumab), types of tumors (melanoma, urothelial carcinoma, esophageal or gastroesophageal junction cancer, or renal cell carcinoma), and PD-L1 status [negative (<1%) or positive (≥1%)], thus indicating that adjuvant therapy with PD-1/PD-L1

adjuvant immunotherapy for cancers is lacking. Furthermore, whether this treatment strategy could be generalizable to more malignant tumors remain uncertain.

inhibitors is efficacious for various solid cancers and is likely to benefit patients regardless of PD-L1 expression levels. Although the exact anti-tumor mechanism remains to be elucidated, the possible reason for the enhanced benefit of adjuvant immunotherapy for patients with cancer may be related to the immune reconstruction by anti-PD-1/PD-L1 treatments after the removal of tumors by surgery (26,27). The findings of the present study supported the use of anti-PD-1/PD-L1 treatments in an adjuvant setting for some types of solid cancers.

Regarding toxicity, the safety and tolerability profile of PD-1/PD-L1 inhibitor monotherapy are well-established in advanced or metastatic cancers (28,29). In the current study, the meta-analysis showed that adjuvant therapy with PD-1/PD-L1 inhibitors was associated with more grade 3 or higher treatment-related AEs and immune-related AEs than placebo (OR=1.63; 95% CI: 1.20-2.21; and P=0.002 and OR=5.86; 95% CI: 2.60-13.25; and P<0.001, respectively). These results were consistent with those of Galsky *et al* (30), who report that pembrolizumab shows more treatment-emergent grade 3-4 AEs (59 vs. 38%) than placebo after first-line chemotherapy in patients with metastatic urothelial cancer. Grade 3 or higher AEs occurred in 59% of patients receiving pembrolizumab and 38% of patients receiving placebo. Naidoo *et al* (28) report that the commonest immune-related AEs of anti-PD-1/PD-L1 antibodies were fatigue, rash, pruritus, pneumonitis, infusion reaction and hypothyroidism and that PD-1/PD-L1 inhibitor monotherapy were well-tolerated. Compared with anti-cytotoxic T lymphocyte antigen 4 antibodies, anti-PD-1/PD-L1 agents were associated with significantly less toxicity. In the current study, although the general safety profile of anti-PD-1/PD-L1 treatments was found to be worse than that of placebo, the rates of grade 3 or higher immune-related AEs were low (7.1-26.7%; Table I) and treatment-related deaths were rarely reported; these findings were consistent with the known AEs reported in previous studies (28-30). The toxicities of PD-1/PD-L1 inhibitors were manageable and well-tolerated.

Despite encouraging results, the present study has several limitations. First, patients in the included trials were diagnosed with different types of tumors (melanoma, urothelial carcinoma, esophageal or gastroesophageal junction cancer and renal cell carcinoma) and tumor stages, thus adding heterogeneity to the analysis. Second, the number of included studies is small (unpublished papers had not been considered) and a limited number of PD-1/PD-L1 inhibitors was included; these may lead to a limitation in the evaluation of results in the current study. Third, in the present study, patients treated with or without prior neoadjuvant chemo-radiotherapy were both eligible. However, because of limited data, a subgroup analysis according to neoadjuvant treatments was not performed. Considering the possible impact of neoadjuvant treatments on survival, future research is needed. Finally, the follow-up time among each trial is different, and the data of OS from some included trials are not mature enough because of the limited follow-up time. Therefore, the analysis of OS needs further investigations.

The current meta-analysis demonstrated that compared with placebo or observation, PD-1/PD-L1 inhibitors greatly enhanced DFS and OS in the adjuvant setting for solid cancers. Although grade 3 or higher treatment-related AEs increased, the toxicities were manageable. The results supported the use of adjuvant therapy with PD-1/PD-L1 inhibitors in some types of solid cancers and this treatment strategy is worth popularizing in clinics. Given the limitations of the present study, further investigations are required.

Acknowledgements

Not applicable.

Availability of data and materials

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

Author's contributions

DM and ZL contributed to the study design and writing. JH and PL performed the data collection and selection. LC and HW performed the data analysis. DM and ZL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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