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Efficacy and safety of immune checkpoint inhibitors in non-small cell lung cancer

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ABSTRACT
Immune checkpoint inhibitors (ICIs) are new therapeutic strategies for non-small cell lung cancer (NSCLC). We aimed to quantitatively evaluate the efficacy and safety of ICIs in NSCLC. Pubmed, Embase, Cochrane Library, and Web of Science were searched for randomized clinical trials comparing ICIs with control therapies in NSCLC. Data were pooled according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. A total of 12 trails comprising 6,919 NSCLC patients were included in this meta-analysis. ICIs therapies significantly improved progression-free survival (PFS) (HR, 0.838; $P < 0.001$), overall survival (OS) (HR, 0.747; $P < 0.001$) and objective response rates (ORR) (RR, 1.311; $P < 0.001$) in NSCLC. Prognostic benefit was observed irrespective of age, sex, treatment line, performance status and histology. Survival improvement of ICIs was limited for NSCLC patients with non-smoker (PFS, $P = 0.468$; OS, $P = 0.317$) or central nervous system (CNS) metastasis (PFS, $P = 0.209$; OS, $P = 0.090$), or positive EGFR mutation (PFS, $P = 0.083$; OS, $P = 0.522$) or PD-L1 expression level less than 5% (PFS, $P = 0.370$; OS, $P = 0.047$). The relative risks of all-grade and high-grade (≥ 3) anemia, neutropenia, leukopenia, thrombocytopenia, stomatitis, nausea, pyrexia, asthenia and neuropathy were all decreased in patients received ICIs compared with control therapies. This meta-analysis provides clinical evidence that ICIs improve PFS, OS, and ORR in NSCLC with fewer adverse effects. Our data establish ICIs as a prefer treatment option for NSCLC patients with smoker, no CNS metastasis, wild type EGFR, and high PD-L1 expression.

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Introduction

Traditional chemotherapy for non-small cell lung cancer (NSCLC) has limited outcomes benefit and the "one size fits all" treatment modality should be changed.[1] Advances of tumor biology promote the development of target therapies. Those targeted drugs block vital cellular signaling pathways, such as vascular endothelial growth factor and epidermal growth factor pathways. But limitations of target therapies should not been ignored. According to our previous studies, about 50% of NSCLC patients have no specific genetic mutations or identifiable targets.[2,3] Limited patients (25%) seem to benefit from targeted therapies.[4] Novel modalities that are effective in a majority of NSCLC patients with less toxicity are urgently needed.

Over the past decades, the findings of immune checkpoint molecules had revolutionized anti-cancer therapies. Immune checkpoint inhibitors (ICIs) could restore anti-tumor immunity, which block immunosuppressive molecules such as programmed cell death protein 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1) and cytotoxic T lymphocyte associated protein 4 (CTLA-4). Currently, ICIs therapies have been novel management options and changed the therapeutic paradigm in NSCLC. Several ICIs have been developed for NSCLC, such as nivolumab, pembrolizumab, atezolizumab, durvalumab, and ipilimumab.[5-9] The clinical efficacy of ICIs in NSCLC, as a part of combination therapies or single agent had been evaluated.[5-11] But the results were inconsistent. A previous meta-analysis reported that ICI immunotherapy is effective for patients with cancers.[12] However, the meta-analysis was across different tumor subtypes, included melanoma, and small cell lung cancer, not focused on NSCLC. Another meta-analysis suggested that ICIs are overall better tolerated than chemotherapy.[13] While, this study did not analyze the survival benefit and tumor response. In a recent meta-analysis, Sheng Z et al.[14] demonstrated that anti-PD-1/PD-L1 therapies could improve the progression free survival (PFS) (HR, 3.20; $P < 0.001$), but not overall survival (OS) (HR, 1.30; $P = 0.180$) compared with control therapies. However, the data resulted from indirect comparisons and excluded anti-CTLA4 therapies. These studies drew different even contradictory conclusions. The efficacy and safety of ICIs in NSCLC remain unclear. Above all, several novel ICIs clinical trials in NSCLC were emerging since then. Pooled analyses of currently available studies may provide clinically useful information and optimize the management of NSCLC. Therefore, we performed this meta-analysis of

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randomized controlled trials (RCTs) to summarize the up to-date evidence.

Methods

Search methods and study selection

Two investigators independently searched the PubMed, EMBASE, Cochrane Library and Web of Science databases with the following key words: "nivolumab", "pembrolizumab", "atezolizumab", "durvalumab", "ipilimumab", "MDX-010", "BMS-963558", "MK-3475", "MPDL3280A", "OPDIVO", "KEYTRUDA", "cancer", or "lung cancer". Reference lists of original articles and reviews were also examined. The articles search was conducted up to 10 September 2017 and language was limited to English. Search results were double-checked by two investigators (Shuai Wang and Jiatao Hao) and the discrepancies were resolved by discussion to validate the accuracy of extraction. Articles from the initial search that match the criteria below were eligible. (1) The studies must be prospective phase II or phase III RCTs to investigate the usage of ICIs in NSCLC. (2) NSCLC must be histopathologically confirmed. (3) None of patients received ICIs treatment before the trials. (4) The reports must analyzed one of endpoints, such as PFS, OS, objective response rate (ORR), and treatment-related adverse effects (AEs). Studies were excluded if (1) patients had benign lung tumor or small cell lung cancer or metastatic cancer from the other organs; (2) data were not provided regarding baseline characteristics of NSCLC patients; (3) trials were not RCTs; (4) case studies, review articles, and animal or in vitro studies; (5) articles were presented only as meeting abstracts without full-text original articles. Reporting of AEs is needed to ensure completeness and transparency of RCTs. This would enable a more precise evaluation of therapeutic risks and benefits. Factors pertinent to the assessment of AEs such as frequency and severity were specifically incorporated into the meta-analysis. Treatment related AEs were assessed by Common Terminology Criteria for Adverse Events (CTCAE 3.0). For evaluation of AEs risk, we calculated RRs and their 95% CIs based on the number of patients with AEs from each RCT. Therefore, trails that did not provide the number of patients with AEs were excluded.

Data extraction and definition

The Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) statements were used to provide complete information of RCTs.[15] All data were independently extracted by two authors according to PRISMA. The primary end point was defined as PFS to standardize data collection. The secondary end points included OS, ORR, and common treatment related AEs. The DFS was defined as the time from random assignment to disease progression and OS time was calculated from random assignment to the date of death from any cause. Tumor response was defined as progressive disease, stable disease, partial response or complete response based on the Response Evaluation Criteria in Solid Tumors criteria.[16] The ORR was defined as the proportion of patients with complete or partial response. Central nervous system (CNS) metastasis of NSCLC at baseline was determined according to criteria reported by previous studies.[8,10] Patients performance status was evaluated by Eastern Cooperative Oncology Group (ECOG) performance status score (on a 5-point scale, with higher numbers indicating greater disability). The quality of RCTs was evaluated based on Jadad scale.[17]

PD-L1 biomarker analysis

The PD-L1 expression was evaluated through immunohistochemical assay using monoclonal anti-human PD-L1 antibody.[5-7] PD-L1 expression should be detected in pretreatment specimens, sush as biopsy and resected samples. Positive PD-L1 expression was defined as staining of the tumor-cell membrane. PD-L1 expression was validated quantitatively at specified level of $< 5\%$, $\geq 5\%$, or $\geq 50\%$ of tumor cells in a section that included at least 100 tumor cells.[5-7] Patients with PD-L1 expression level of at least 5% included those with PD-L1 expression level of at least 50%.

Statistical analysis

The choice of fixed or random-effects model was determined through Mantel-Haenszel method. Sensitivity analyses were performed by excluding each study at a time individually. The publication bias was assessed by Begg's funnel plots and Egger's linear regression test. $P < 0.05$ was defined as significant publication bias. Meta regression with random-effects model was performed to evaluate potential effects of clinical variables on outcomes. The restricted maximum likelihood method was carried out to evaluated the residual between-trial variance and heterogeneity degree. Monte Carlo permutation test was performed with 10,000 random permutations.[18] Stata 11.0 (Stata Corporation, College Station, TX, USA) was used in this meta-analysis. Differences were considered statistically significant at two sided $P < 0.05$.

Results

Eligible studies and characteristics

Our initial search retrieved 724 references. After carefully screening abstract and full text of references, 12 trails were finally included.[5-11,19-23] The selection steps were summarized in the flow diagram (Figure 1). These 12 RCTs enrolled a total of 6,919 NSCLC patients (ICIs arm: 3,598, control arm: 3,321). Among 12 RCTs, 7 were anti-PD-1 (4 on nivolumab;[5,19-21] 3 on pembrolizumab,[6,10,22]) 3 were anti-PD-L1 (2 on atezolizumab;[7,23] 1 on durvalumab,[8]) and 2 were anti-CTLA-4 (2 on ipilimumab.[9,11]) These studies comprised 3 phase II, 1 phase II/III and 8 phase III clinical trials. ICIs were compared with placebo in one study. Eight studies were ICIs versus chemotherapy and 2 studies were chemotherapy plus ICIs versus chemotherapy alone. The trial quality was quite good with Jadad score of 5 in all RCTs. The characteristics of 12 RCTs were listed in Supplementary Table S1.

Progression free survival

Twelve studies reported the PFS of NSCLC patients. Heterogeneity analysis revealed that there was significant between-study heterogeneity (chi-squared = 54.05, $P < 0.001$, I-squared = 75.9%). A statistically significant PFS improvement was observed in ICIs arm (HR, 0.838; 95% CI, 0.796 – 0.882; $P < 0.001$) (Figure 2). Subgroups analyses were performed based on the target, drug and

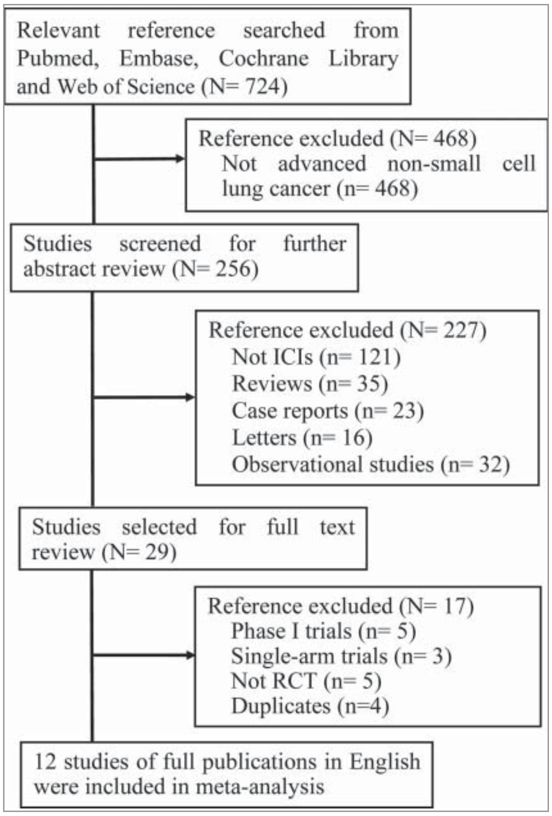

Figure 1. Flow diagram of study selection.

regimen (Supplementary Table S2). Significant PFS benefits were found in all targets, including anti-PD-1 (HR, 0.844; 95% CI, 0.792-0.901), anti-PD-L1 (HR, 0.812; 95% CI, 0.726-0.907), and anti-CTLA-4 (HR, 0.847; 95% CI, 0.744-0.963). A statistically significant PFS improvement was observed in both ICIs monotherapies (HR, 0.840; 95% CI, 0.794-0.889) and combination therapies of ICIs with chemotherapy (HR, 0.825; 95% CI, 0.728-0.936) (Figure 2). We further performed meta-regression by the clinical variables. As shown in Supplementary Table S2, target (P = 0.879), drug (P = 0.776) and regimen (P = 0.634) did not result in the inter-study heterogeneity.

Overall survival

The meta-analysis of OS was based on 12 RCTs provided the required data. Between-study heterogeneity was significant (chi-squared = 32.89, P = 0.002, I-squared = 60.5%). There was significant OS improvement in ICIs arm compared with control arm (HR, 0.747, 95% CI, 0.703-0.795) (Figure 3). In stratified analyses by target, significant OS benefit was found in anti-PD-1 (HR, 0.726; 95% CI, 0.670-0.786), and anti-PD-L1 (HR, 0.679; 95% CI, 0.595-0.775), not in anti-CTLA-4 (HR, 0.915; 95% CI, 0.794-1.053) (Figure 3). Meta regression suggested that target (P = 0.200), drug (P = 0.451) and regimen (P = 0.057) did not alter the pooled HR significantly (Supplementary Table S2).

Selected subgroups

Survival benefit was explored across specified subgroups, according to baseline clinicopathologic features of NSCLC patients. Notably, PFS and OS benefit of ICIs was observed irrespective of sex, age, treatment line and ECOG performance status (Table 1). Survival HRs favored ICIs compared to control therapies in NSCLC patients with former/ current smoker (PFS, $P < 0.001$; OS, $P < 0.001$), but disfavored ICIs in NSCLC patients who had never smoked (PFS, P = 0.468; OS, P = 0.317). Squamous NSCLC had slightly lower HR of death than non-squamous NSCLC (PFS, 0.715 VS. 0.786; OS, 0.694 vs. 0.805), although this comparison was not powered by statistical analysis. NSCLC patients without CNS metastases seemed to derive more survival benefit from ICIs than control therapies (PFS, $P < 0.001$; OS, $P < 0.001$). Conversely, patients with CNS metastases disease received similar survival benefit from ICIs and control therapies (PFS, $P = 0.209$; OS, $P = 0.090$). Survival improvement was also evident in patients with negative EGFR mutation (PFS, $P < 0.001$; OS, $P < 0.001$), not in those with positive EGFR mutation (PFS, $P = 0.083$; OS, $P = 0.522$).

As shown in Table 1, survival benefit from ICIs increased with increasing PD-L1 expression on tumour cells. Survival improvement was significant in NSCLC patients with PD-L1 expression in at least 5% of cells (PFS, $P = 0.003$; OS, $P < 0.001$) and at least 50% of cells (PFS, $P < 0.001$; OS, $P < 0.001$). In the exploratory subgroup analysis involving patients with PD-L1 expression level of <5%, the HR for DFS was 0.911 (95% CI, 0.742-1.118), and HR for OS was 0.854 (95% CI, 0.730-0.998).

Overall response rate

Eleven RCTs provided information in detail about ORR. The pooled results showed ICIs significantly improved ORR (RR, 1.311; 95% CI, 1.205-1.428; $P < 0.001$) (Supplementary Fig. S1). However, better ORR was only found in anti-PD-1 (RR, 1.778; 95% CI, 1.535-2.059), and anti-PD-L1 (RR, 1.250; 95% CI, 1.082-1.443), not in anti-CTLA-4 (RR, 1.008; 95% CI, 0.868-1.170). In stratified analyses regarding individual drug, three ICIs (nivolumab, pembrolizumab and durvalumab) resulted in significant ORR improvement. Two agents (atezolizumab and ipilimumab) did not improve ORR (Supplementary Table S2). Subgroup analysis showed that both ICIs monotherapies and combination therapies improved ORR. Meta regression indicated that none of the examined factors were responsible for between-study heterogeneity on ORR, including target ($P = 0.064$), drug ($P = 0.076$) and regimen ($P = 0.552$).

Treatment related adverse events

The common AEs were summarized in Table 2. The pooled analyses showed that the risks of all grade anemia, neutropenia, leukopenia, thrombocytopenia, anorexia, stomatitis, nausea, pyrexia, asthenia, myalgia, alopecia and neuropathy were lower in patients receiving ICIs. The pooled RR indicated the risks of all-grade diarrhea (RR, 1.053; 95% CI, 0.874-1.269) were comparable between ICIs and control group. However, the risks of all-grade ALT/AST increased ($P < 0.001$), pruritus ($P < 0.001$), rash ($P < 0.001$) and thyroid dysfunction ($P < 0.001$) were higher in patients treated with ICIs than those in control group.

To clarify the severity of AEs, we further analyzed the risks of $\geq$ 3 grade AEs. Compared with the control group, the ICIs group showed a lower incidence of $\geq$ 3 grade anemia,

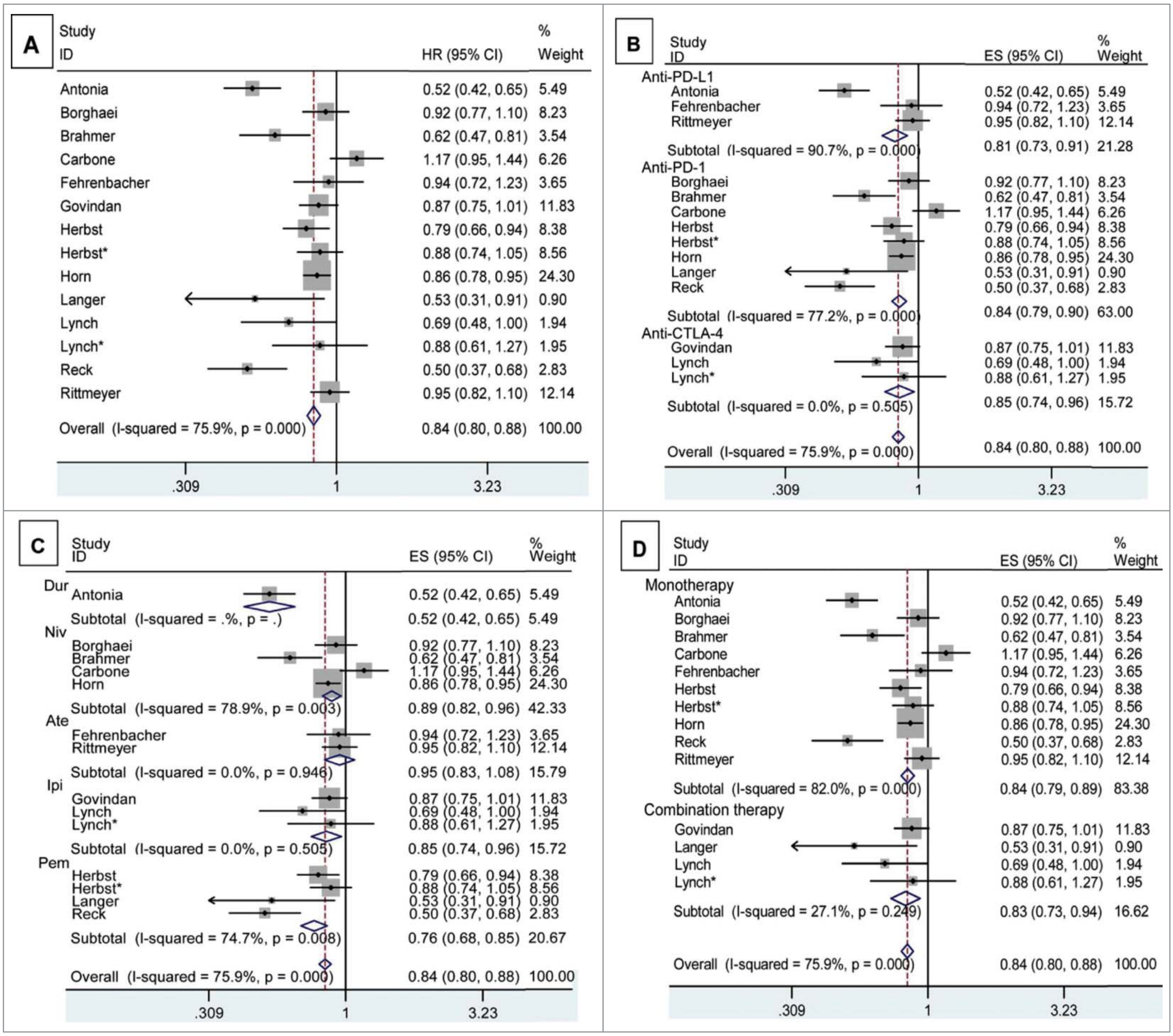

Figure 2. The pooled analyses of progression free survival of NSCLC patients who received ICIs compared to control therapies (A) based on target (B), drug (C) and regimen (D). The number of subjects with available survival information in ICIs or control arm is 3,598 and 3,321, respectively. Patients number in different subgroups was shown in Supplementary Table S2. Squares indicate study-specific HR (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; diamond indicates the summary HR estimated with its 95% CI.

neutropenia, leukopenia, stomatitis, pyrexia, asthenia. Patients receiving ICIs experienced a comparable risk of $\geq$ 3 grade thrombocytopenia ($P = 0.052$), anorexia ($P = 0.140$), diarrhea ($P = 0.075$), nausea ($P = 0.181$), myalgia ($P = 0.944$), alopecia ($P = 0.494$), pruritus ($P = 0.303$), rash ($P = 0.060$), neuropathy ($P = 0.439$), and thyroid dysfunction ($P = 0.810$) (Table 2). Only the risks of $\geq$ 3 grade ALT/AST increased (RR, 4.451; 95% CI, 1.777-11.146; $P = 0.001$) were higher in ICIs arm than control arm (Table 2).

Sensitivity analyses and publication bias

We carried out sensitivity analyses to assess the stability of the results. The leave-one-out sensitivity analyses indicated that no individual study changed the pooled data qualitatively. The shapes of the funnel plots seemed symmetrical in all pooled analyses, suggesting the absence of publication bias. Z-value (continuity corrected) of Begg's test in the meta-analyses was 1.64 on PFS ($P = 0.101$), 0.33 on OS ($P = 0.743$), and 1.40 on ORR ($P = 0.161$). Egger's test showed that the t value (bias) of the pooled analyses was -1.67 on PFS ($P = 0.121$), -0.27 on OS ($P = 0.793$), and -2.05 on ORR ($P = 0.064$). As shown in Supplementary Table S2, Begg's test and Egger's test indicated no significant publication bias in subgroup analyses. We did not perform non-parametric "trim-and-fill" method, because publication bias might not have a significant influence on the results.

Discussion

This study with updated data improved our understanding about the efficacy and safety of ICIs in NSCLC. Our data showed that ICIs had superior PFS, OS and ORR with improved safety profile compared with conventional therapies. Immunological checkpoints are inhibitory feedback loops of immune system to mitigate uncontrolled propagation of immune responses and maintain selftolerance. Those

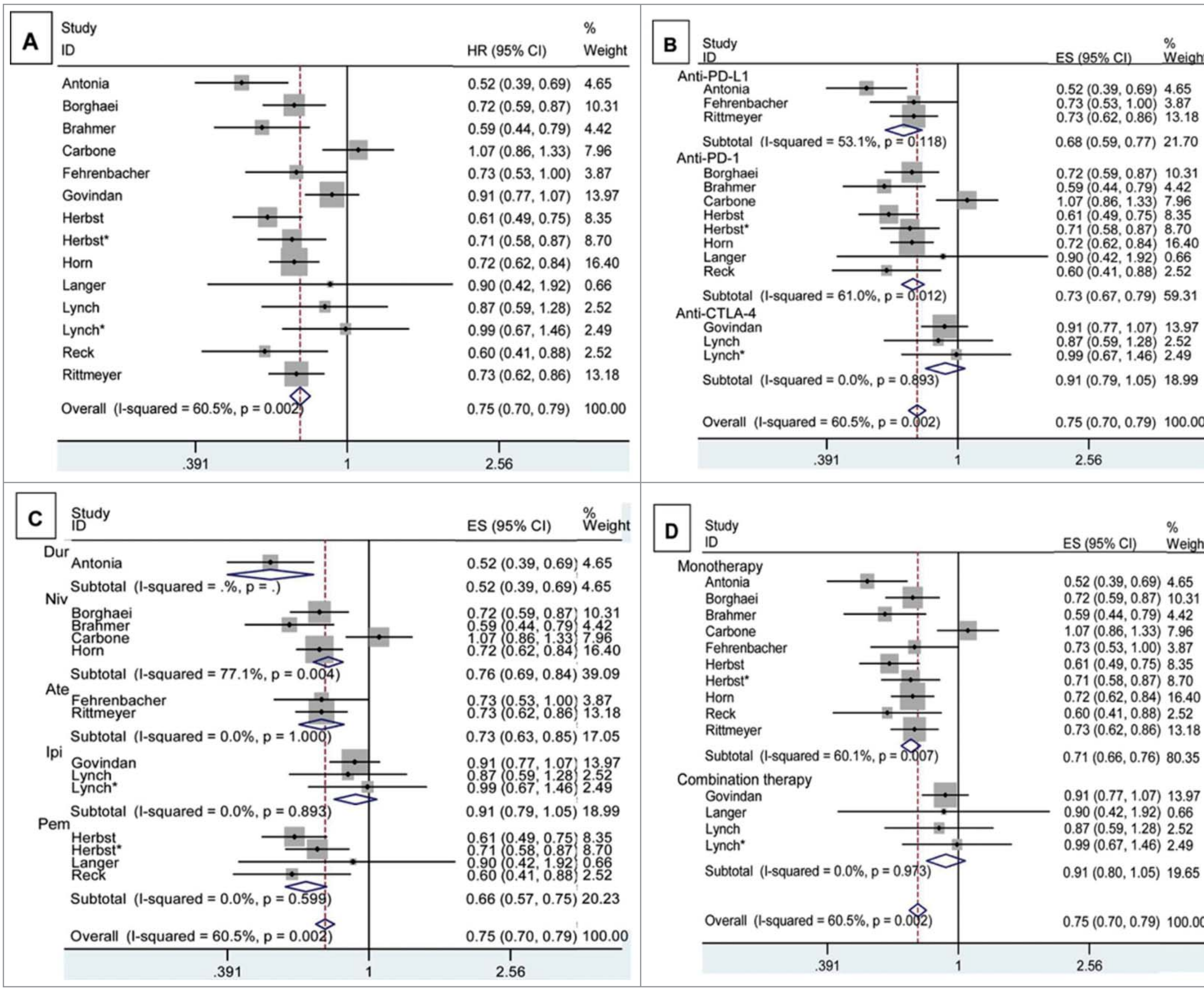

Figure 3. The pooled analyses of overall survival of NSCLC patients who received ICIs compared to control therapies (A) based on target (B), drug (C) and regimen (D). The number of subjects with available survival information in ICIs or control arm is 3,598 and 3,321, respectively. Patients number in different subgroups was shown in Supplementary Table S2. Squares indicate study-specific HR (size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CI; diamond indicates the summary HR estimated with its 95% CI.

checkpoints contributes co-stimulatory pathways (CD28, ICOS) and co-inhibitory pathways (CTLA-4, PD-1).[24] ICIs restore intrinsic functions of dampening effector T cells, thus enhance anti-tumour immunity. More specifically, ICIs trigger tumor infiltrating lymphocytes (TILs) in tumor microenvironment by induction of interferon-γ and cytokines.[25]

This meta-analysis showed that ICIs were associated with significant prolonged PFS and OS. It has been observed that target, drug or regimen did not significantly alter survival benefit of ICIs (Supplementary Table S2). Our results were strengthened by the meta-regression analyses and sensitivity analyses. In a stratified analysis based on drug, a positive effect of ICIs for PFS was not observed in atezolizumab (Figure 2). However, these data were insufficient to draw definite conclusions, because only two studies performed the PFS analyses of atezolizumab. Regarding OS, subgroup analyses showed anti-CTLA-4 and ipilimumab had no obvious benefit compared with control therapies (Figure 3). Those findings may reduce statistical power to get reliable results. Although meta regression suggested target, drug and regimen did not change the overall results significantly, our results regarding OS should be interpreted with very caution.

One interesting question attracted our attention: why survival improvement of anti-CTLA-4 is not consistent with anti-PD-1 and anti-PD-L1. One possible explanation is that roles of CTLA-4 are different from those of PD-1 and PD-L1. CTLA-4 is expressed mainly on T cells and provide inhibitory signals in the initial activation of T cells, typically in lymphoid tissues.[26,27] PD-1 and PD-L1 is expressed on B, T, myeloid cells, as well as non-lymphoid organs.[28] The PD-1 pathway primarily inhibits effector T cells at the later stage of inflammatory responses, typically in peripheral tissues. Another possible explanation is that the mechanisms underlying the anti-tumour activity are different. CTLA-4 blockade could increase diversity of T cells pool.[29] Anti-tumour activity of PD-1 blockade relies on immune function restoration of peripheral T cells. Specific PD-L1 inhibition would block PD-1:PD-L1 and PD-L1:CD80 interactions, and preserve PD-1:PD-L2 interactions.[30] In theory, there are many differences in timing and location of immune checkpoint among CTLA-4, PD-1 and PD-L1 blockage therapies. Thus, further studies with functional analyses are needed to address this issue.

As suggested by exploratory analyses, survival improvement of ICIs may be driven by certain subgroups of

Table 1. Exploratory subgroup analyses of survival in the intent-to-treat population.

Variables		PFS		OS	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male	0.719 (0.648 – 0.798)	< 0.001	0.768 (0.699 – 0.845)	< 0.001
	Female	0.905 (0.822 – 0.986)	0.046	0.791 (0.686 – 0.912)	0.001
Age	< 65 yrs	0.768 (0.688 – 0.858)	< 0.001	0.759 (0.675 – 0.855)	< 0.001
	≥ 65 yrs	0.870 (0.747 – 0.982	0.042	0.776 (0.664 – 0.907)	0.001
Line	1	0.850 (0.769 – 0.941)	0.002	0.920 (0.822 – 0.989)	0.043
	≥ 2	0.833 (0.785 – 0.884)	< 0.001	0.683 (0.635 – 0.735)	< 0.001
ECOG	0	0.795 (0.668 – 0.947)	0.010	0.780 (0.677 – 0.898)	0.001
PS	1	0.741 (0.656 – 0.837)	< 0.001	0.731 (0.668 – 0.801)	< 0.001
Smoking status	Non-smoker	1.118 (0.817 – 1.528)	0.468	0.868 (0.657 – 1.146)	0.317
	Former/ current smoker	0.690 (0.605 – 0.788)	< 0.001	0.697 (0.614 – 0.791)	< 0.001
Histology	Squamous	0.715 (0.598 – 0.856)	< 0.001	0.694 (0.604 – 0.797)	< 0.001
	Non-squamous	0.786 (0.682 – 0.905)	0.001	0.805 (0.723 – 0.897)	< 0.001
CNS metastasis	Yes	0.739 (0.461 – 1.185)	0.209	0.735 (0.515 – 1.049)	0.090
	No	0.740 (0.642 – 0.853)	< 0.001	0.678 (0.605 – 0.759)	< 0.001
EGFR mutation	Positive	1.358 (0.960 – 1.919)	0.083	1.115 (0.799 – 1.557)	0.522
	Negative	0.722 (0.636 – 0.819)	< 0.001	0.682 (0.602 – 0.773)	< 0.001
PD-L1 expression	< 5%	0.911 (0.742 – 1.118)	0.370	0.854 (0.730 – 0.998)	0.047
	≥ 5%	0.806 (0.700 – 0.928)	0.003	0.656 (0.575 – 0.748)	< 0.001
	≥ 50%	0.695 (0.589 – 0.821)	< 0.001	0.549 (0.462 – 0.653)	< 0.001

patients. Our data showed NSCLC patients with non-smoker or positive EGFR mutation did not acquire survival benefit from ICIs. Previous study indicated NSCLC patients who never smoking had low levels of mutational burdens and heterogeneity.[31] While, tumors bearing high levels of somatic mutations are related to high sensitivity of immune-checkpoint inhibitors.[31] EGFR activation results in suppression of anti-tumor immune response through induction of regulatory T cells or reduction of T cells chemoattractant. Akbay et al.[32] had demonstrated that active EGFR mutation could upregulate PD-L1 expression and facilitate evasion of tumor cells from immunity. Retrospective studies have identified several markers associated with outcomes, including TIL count, ICOS, and NY-ESO-1.[33] In CheckMate 026, Carbone DP et al.[20] reported NSCLC patients with PD-L1 expression level of 5% did not benefit from nivolumab compared with chemotherapy. However, several trials indicated nivolumab could prolong PFS or OS of NSCLC patients with PD-L1 expression level of 5%.[5,19,21] Many factors appeared to have influence on the treatment efficacy of nivolumab. In CheckMate 026, imbalances of clinicopathological features at baseline may disfavored the ICIs group, including higher ratio of metastases, higher tumor burden, and lower proportion of women in ICIs group than chemotherapy group. These disease characteristics related to worse outcomes of NSCLC patients. In addition, low tumor mutation burden also favored the chemotherapy group in CheckMate 026.[20] In this meta analysis of RCTs, we found that PD-L1 expression levels offered the potential for identifying patients benefited from ICIs (Table 1). Although PD-L1 negative tumors response to ICIs, improved outcomes could not been seen in many studies.[5,7,19,21] Thus, these NSCLC patients received ICIs should be further evaluated with cautions. Much effort at

Table 2. Relative Risk of Treatment-related Common Adverse Events in NSCLC Patients Treated with ICIs Compared to Control Therapies.

Adverse events	All grades		Grade ≥ 3	
	RR (95% CI)	P	RR (95% CI)	P
Anemia	0.491 (0.411 – 0.587)	< 0.001	0.639 (0.464 – 0.881)	< 0.001
Neutropenia	0.245 (0.196 – 0.306)	< 0.001	0.237 (0.184 – 0.307)	< 0.001
Leukopenia	0.289 (0.209 – 0.400)	< 0.001	0.169 (0.095 – 0.301)	< 0.001
Thrombocytopenia	0.627 (0.494 – 0.795)	< 0.001	0.659 (0.433 – 1.002)	0.052
ALT/AST increased	2.353 (1.608 – 3.443)	< 0.001	4.451 (1.777 – 11.146)	0.001
Anorexia	0.801 (0.658 – 0.974)	0.026	0.542 (0.240 – 1.224)	0.140
Diarrhea	1.053 (0.874 – 1.269)	0.586	1.640 (0.952 – 2.824)	0.075
Stomatitis	0.182 (0.109 – 0.304)	< 0.001	0.149 (0.027 – 0.830)	< 0.001
Nausea	0.513 (0.429 – 0.614)	< 0.001	0.480 (0.163 – 1.408)	0.181
Pyrexia	0.627 (0.455 – 0.865)	0.004	0.077 (0.026 – 0.227)	< 0.001
Asthenia	0.714 (0.626 – 0.814)	< 0.001	0.430 (0.282 – 0.655)	< 0.001
Myalgia	0.457 (0.316 – 0.661)	< 0.001	0.932 (0.132 – 6.598)	0.944
Alopecia	0.244 (0.172 – 0.347)	< 0.001	0.328 (0.013 – 7.985)	0.494
Pruritus	4.614 (3.013 – 7.064)	< 0.001	2.382 (0.456 – 12.439)	0.303
Rash	2.370 (1.792 – 3.134)	< 0.001	2.547 (0.962 – 6.745)	0.060
Neuropathy	0.556 (0.433 – 0.713)	< 0.001	0.723 (0.317 – 1.646)	0.439
Thyroid dysfunction	12.857 (5.564 – 29.710)	< 0.001	1.481 (0.061 – 36.219)	0.810

ALT: alanine aminotransferase; AST: aspartate aminotransferase. Incidence rates of treatment-related AEs occurring in ≥5% of patients by common terminology criteria for adverse events (version 3).

identifying biomarkers is needed to gain utmost benefit or avoid unnecessary treatment.

ORR analyses demonstrated that patients receiving ICIs had better disease control than those in control groups. It should be noted that anti-tumour efficacy of ICIs are indirect, relied on the activities of immune effector cells. While most conventional chemotherapies directly diminish tumors. The kinetics of tumor responses therefore differ significantly. Tumor volumes could not been shrunk until ICIs restart effective anti-tumor immune. Tumor responses potentially need longer time to become clinical detectable compared with conventional chemotherapies.[24] In addition, ICIs induce infiltration of activated T cells into the tumor. The inflammation and edema occur in tumor tissues. So, tumour volumes would initially increase but subsequently pseudo-progression translates into tumour shrinkage. Therefore, tumor responses evaluation by RECIST may be inappropriate. Alternative immune-related response criteria (irRC) had been proposed.[34,35] Overall tumour burden is the indicator of clinical responses compared with the baseline lesion measurements. Based on irRC, new lesions do not mean disease progression if net tumour burden is stable. Durable stable disease is considered as clinical activity of immunotherapies. The irRC make good theoretical and clinical sense. But further prospective validation is needed.

The clinical trials of ICIs have raised concerns over treatment related AEs. In the present meta-analysis, we found the spectrum of ICIs associated AEs were consistent with previous studies.[36-38] Overall, low risks of all-grade anemia, neutropenia, leukopenia, thrombocytopenia, anorexia, stomatitis, nausea, pyrexia, asthenia, myalgia, alopecia and neuropathy were observed in ICIs compared to control therapies. However, ICIs had a higher incidence of all-grade ALT/AST increased ($P < 0.001$), pruritus ($P < 0.001$), rash ($P < 0.001$) and thyroid dysfunction ($P < 0.001$). ICIs cause AEs with potential immunologic etiologies, so-called immune-mediated AEs. These AEs include rash or pruritus, gastrointestinal disorders, and endocrinopathies. The ALT/AST increased, pruritus, and rash are natural responses to ICIs with enhanced immunity and higher cytokines. Theoretically, those reactions could be due to non-specific activation of antigen presenting cells, rapid pro liferation of T cells and reduced Treg mediated immunosuppression.[37] Thyroid dysfunction may be a consequence of ectopic expression of CTLA-4, PD-L2 blockage and high level of IL-2.[38,39] Interestingly, occurrence of treatment-related dermatologic AEs is associated with better tumor response and survival benefit in cancer patients received ICIs.[39,40] However, it is unclear whether treatment-related endocrine AEs are associated with prognostically favorable outcomes.

Preclinical studies indicated that both chemotherapy and radiotherapy induced PD-L1 expression on tumor cells and modulated the immunity against tumor cells.[41,42] Chemotherapy and radiotherapy could kill tumor cells and create a pool of antigen for crosspresentation. Thereby, conventional therapies enhance immunogenicity and induce inflammation. Fiorica F et al.[43] had demonstrated that combination of radiotherapy and ICIs obtained OS and PFS benefit without an increase in toxicities in NSCLC patients. Significant survival improvement was also observed in NSCLC with combination treatment of ICIs and chemotherapy.[10,11] Our study also showed combination of chemotherapy and ICIs could prolong survival and improve tumor response (Supplementary Table S2). Previous studies reported synergistic treatment of anti-PD-1 and anti-CTLA-4 had high response rate and durable response with tolerable safety profile.[44,45] These exploratory investigations showed encouraging clinical activity and feasibility of combination therapies. New combinations of ICIs with classical chemotherapy and/or radiotherapy will further revolutionize the treatment of NSCLC. This meta-analysis reported our interesting preliminary findings. We will do further research and validate the clinical relevance of combination therapies in other validation sets.

In this study, several limitations need to be addressed. This meta analysis was based on study-level evidence. More reliable results could been draw from individual patient data-based study. Second, our conclusions came from the sum of 12 RCTs with between-study heterogeneity. Inconsistent HRs for different targets and drugs should be noticed. The inclusion and exclusion criteria differed from each trial. In this study, positive effects of ICIs for PFS and OS were observed in both first line treatment and $\geq$ second line treatment. However, patients with $\geq$ second line treatment of ICIs might have different clinical outcomes, compared to those with first line treatment of ICIs (Table 1). The criteria related to previous treatment (ie. chemotherapy or chemo-radiotherapy) might affect the results. Heterogeneous inclusion and exclusion criteria of treatments should be considered. In addition, confounding factors (the use of glucocorticoid and post-progression treatment) should also be incorporated into analyses. However, the effects of other drugs (ie. glucocorticoid) and post-progression treatment on outcomes were not available in including trials. We could not extract the HRs and perform pooled analyses. Due to lack of original data, we did not perform subgroup analyses based on key molecular markers (ie. ROS, ALK, and KRAS status or overall mutation loads) to identify the exact benefit population. And exploratory subgroup analyses were not conducted in different tumor stage and dosing groups. Therefore, further researches with complete information of required data from individual patient are needed to clarify the efficacy and safety of ICIs.

Taken together, this meta-analysis provided direct clinical evidence supporting the notion that ICIs had superior survival benefit over control therapies in NSCLC, especially for those patients with smoker, no CNS metastasis, wild type EGFR, and high PD-L1 expression. The outcomes appear very promising and treatment-related AEs were acceptable. Our observations support further larger scale multicenter RCTs to rigorously evaluate the long-term efficacy and safety of ICIs in NSCLC.

Conflict of interest statement

No potential conflicts of interest were disclosed.

Author contributions

Conceptualization: Shuai Wang and Lijie Tan; Methodology and validation: Shuai Wang, Hao Wang, Yong Fang and Lijie Tan; Data analysis: Jiatao Hao and Shuai Wang; Writing: Shuai Wang; Supervision: Hao Wang, Yong Fang and Lijie Tan.

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