BMJ Open Predictive effect of molecular and clinical characteristics for the OS and PFS efficacy of anti-PD-1/PD-L1 immunotherapy in patients with NSCLC: a meta-analysis and systematic review

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ABSTRACT

Objective To evaluate the predictive effect of molecular and clinical characteristics for the efficacy of anti-programmed cell death 1 (PD-1)/programmed cell death ligand-1 (PD-L1) immunotherapy in patients with non-small cell lung cancer (NSCLC).

Design Systematic review and meta-analysis.

Setting Twelve randomised controlled trials (RCTs) with 7442 patients were retrieved from all over the world.

Methods Electronic databases were searched for eligible RCTs. The HRs and 95% CIs for overall survival (OS) and progression-free survival (PFS) for the whole and subgroup population were extracted for meta-analysis using Review Manager V.5.3 software.

Primary and secondary outcome measure OS was the primary outcome and PFS was the secondary outcome.

Results Twelve RCTs with 7442 patients were included. For the trial population, anti-PD-1/PD-L1 immunotherapy significantly improved OS (HR=0.78, 95% CI 0.70 to 0.86, $p<0.00001$) and objective response rate (ORR) (risk ratio=1.37, 95% CI 1.08 to 1.74, $p=0.009$). Subgroup analysis results showed an improved OS at PD-L1 $\geq$ 1%, $\geq$ 5% and $\geq$ 50% levels, and a longer PFS at PD-L1 $\geq$ 5% and $\geq$ 50% levels. Moreover, OS and PFS benefits were observed in the non-first line treatment, squamous cell carcinoma histology, male, smoking, non-central nervous system (CNS) metastasis, epidermal growth factor receptor (EGFR) wild-type and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutant subgroups.

Conclusions Anti-PD-1/PD-L1 immunotherapy significantly improved OS and ORR and reduced the rate of Adverse Events (AEs) compared to chemotherapy. PD-L1 expression, line of therapy, histology, sex, smoking history, CNS metastases, EGFR and KRAS mutational status might be potential predictors for the therapeutic effect of anti-PD-1/PD-L1 immunotherapy in specific patients with NSCLC.

INTRODUCTION

Lung cancer (LC) is a malignant disease that caused by the uncontrolled cell growth

Strengths and limitations of this study

- This meta-analysis comprehensively evaluated the predictive effect of the molecular and clinical characteristics for the efficacy of anti-programmed cell death 1 (PD-1)/programmed cell death ligand-1 (PD-L1) immunotherapy in patients with non-small cell lung cancer and helped clinicians to effectively select patients who may benefit from PD-1/PD-L1 inhibitors.
- The methods used to quantify PD-L1 were different in the included trials, influencing the PD-L1 expression results in the subgroup analysis.
- HRs and corresponding 95% CIs were directly extracted from the original studies, and no individualised data were used for analysis, which could be a source of reporting bias.
- The sample size of some subgroups (central nervous system metastasis status, epidermal growth factor receptor mutation status and Kirsten rat sarcoma viral oncogene homolog mutational status) was too small and could have influenced the results of subgroup meta-analysis.

of abnormal lung cells. Globally, LC has become the most common cancer regarding incidence and mortality.¹ Small-cell and non-small cell lung cancer (SCLC and NSCLC) represent two major types of LC, accounting for 15% and 85% of all patients.² Most of the patients with NSCLC are already symptomatic when diagnosed, presenting with advanced or metastatic disease stage, and the prognosis is often poor. Conventional treatment strategies are often ineffective and have been associated with very low survival rates.³ In the past, platinum-based chemotherapy has been the preferred option for advanced-stage patients with NSCLC without known actionable mutations. However,

chemotherapy only offers modest survival benefits and a limited safety profile.⁴ More recently, specific monoclonal antibodies targeting cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and its ligands programmed cell death ligand-1 (PD-L1) and PD-L2, known as immune checkpoint inhibitors (ICIs), have been successfully used to treat many solid tumours, including LC.⁵ PD-1 is a receptor expressed on activated T cells, B cells and natural killer T cells. When PD-1 is combined with PD-L1/PD-L2, the T-cell activity is inhibited and tumour-induced immune suppression is promoted.⁶ PD-L1 is a protein expressed in tumour cells and tumour-infiltrating immune cells. When PD-L1 binds to PD-1 and B7-1, the antitumour function of T cells will be downregulated.⁷ Accordingly, blocking the interactions of PD-L1–PD-1 and PD-L1–B7-1 can restore T cell's antineoplastic function and activation. Compared with traditional chemotherapy, immunotherapy that targets the PD-1–PD-L1 axis can significantly enhance OS and PFS in advanced patients with NSCLC; some of these antibodies have been approved to treat metastatic patients with NSCLC by the US Food and Drug Administration (FDA).^{8–10} Although ICIs have led to new horizons in the treatment of NSCLC, few patients who received ICIs treatment benefited from it. Thus, it is critical to determine which patients are most likely to respond to ICIs.

In the present study, we comprehensively assessed the effect of anti-PD-1/PD-L1 immunotherapy versus chemotherapy in patients with NSCLC. Furthermore, subgroup analysis was conducted to evaluate the association between PD-L1 expression level, histology, line of therapy, age, sex, smoking history, central nervous system (CNS) metastasis, Eastern Cooperative Oncology Group performance status (ECOG PS), epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutational status and the clinical effect of anti-PD-1/PD-L1 immunotherapy. Herein, we sought to explore molecular and clinical characteristics that can effectively predict the clinical efficacy of ICIs, and guide clinical decision-making.

METHODS

Eligibility criteria

This study was conducted in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.

Retrieval strategy

Eight databases including PubMed, EMbase, The Cochrane Library, clinicaltrial.gov, CNKI (China National Knowledge Infrastructure), WanFang database, VIP database (China Science and Technology Journal Database) and CBM database (China Biology Medicine disc) were comprehensively retrieved to collect studies up to 18 August 2020. The keywords used in the literature search

included: “PD-1/PD-L1 inhibitor”, “Immune Checkpoint Inhibitor”, “Anti-PD-1”, “Anti-PD-L1” and “Nivolumab”, “Pembrolizumab”, “Atezolizumab”, “Avelumab”, “Durvalumab” and “Lung cancer”. Please see online supplemental files for the full search strategy.

Inclusion and exclusion criteria

The inclusion criteria consisted of: (1) The study must be a prospective randomised controlled trial (RCT); (2) the study must evaluate the clinical efficacy of anti-PD-1/PD-L1 immunotherapy and chemotherapy in patients with LC; (3) the study must report the overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and Adverse Events (AEs); (4) the HRs and risk ratios (RRs) with 95% CIs for OS and PFS and data including age, sex, histology, smoking status, PD-L1 expressing status, ECOG PS, EGFR and KRAS mutation status can be drawn out from the text. Exclusion criteria included: (1) retrospective or prospective observational cohort studies; (2) phase I trials; (3) reviews, meta-analysis, letters, case reports, conference abstracts, expert opinions, cell and animal experiments; (4) duplicate publications; (5) studies with insufficient data; (6) participants have inconsistent baselines. If multiple articles published the same study, the most recent or complete one was used.

Data extraction and quality assessment

Two authors (RA and FZ) independently extracted and reviewed the data from the included studies, and points of disagreement were reconciled by a discussion with the third author. The collected information included: first author, publication year, ClinicalTrials.gov number, trial phase, number of patients, therapeutic strategy, clinical effect, adverse events, and related molecular and clinical characteristics (including pathological type, PD-L1 levels, line of therapy, age, sex, smoking status, CNS metastasis, ECOG performance status, EGFR mutation status, KRAS mutation status). Methodological quality evaluation was carried out according to the Cochrane Risk of Bias Tool.¹¹ We rated each study as high, low, or unclear risk of bias according to the seven criteria: random sequence generation; allocation concealment; blinding of participants and personnel to the study protocol; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias. Two authors (RA and FZ) independently conducted the quality assessment, any controversies were settled through discussing with a third author.

Patient and public involvement

No patient involved.

Statistical analysis

The Cochrane Review Manager (RevMan) software (V.5.3) was used to perform the meta-analysis. Heterogeneity of all involved trials were examined using the I^2 statistic and Q statistic. If no heterogeneity existed ($p > 0.1$; $I^2 < 50\%$), a fixed-effects model was used. In case of significant heterogeneity, the use of a random-effects model

Figure 1 Flowchart of study selection procedure. VIP: China Science and Technology Journal Database. CBM, China Biology Medicine; CNKI, China National Knowledge Infrastructure.

was considered. And we also performed a meta-regression models to better understand the sources of heterogeneity. The pooled HRs with 95% CIs for OS and PFS and the RRs with 95% CIs for ORR and AEs were calculated. The pooled HRs > 1 for OS and PFS preferred the chemotherapy group, while the pooled HRs < 1 preferred the anti-PD-1/PD-L1 immunotherapy group. RR > 1 for ORR and AEs indicated a higher response rate and toxicity, while RR < 1 was the opposite. $P < 0.05$ was considered statistically significant.

RESULTS

Search results and study characteristics

Up to 18 August 2020, our search strategy identified a total of 2433 trials. 180 studies were excluded for duplications, 1834 studies including reviews, meta-analyses, letters, case reports, conference papers, ongoing trials were excluded. After screening the title and abstracts, 365 trials were excluded because they did not meet the inclusion criteria. We comprehensively screened the full text of the remaining 54 studies and finally selected 12 RCTs for the final analysis. The detailed search and study selection process was shown in figure 1. A total of 7442 patients with stage III or IV NSCLC^{12–23} were included in our study. The 12 included trials included: 10 phase III studies, 1 phase II/III study and 1 phase II study; 4 trials evaluated pembrolizumab, 4 trials assessed nivolumab, 2 trials assessed atezolizumab, avelumab and durvalumab

were each evaluated in one study. Detailed features of each trial were summarised in table 1.

Quality assessment and publication bias

All the selected trials were RCTs, and the methodological quality of all included studies were generally good (online supplemental figure S1A). Moreover, the main problem influencing the studies' quality was the absence of blinding since all studies were open-labelled. The funnel plots of the included trials revealed no substantial publication bias (online supplemental figure S1B,C).

Meta-regression analysis

Due to the high I^2 in our analysis, we performed meta-regression analysis to identify the sources of heterogeneity. However, we did not find the source of heterogeneity among the common factors, such as patient's number, line of therapy, phase of trial, tumour stage, experimental arms, control arms and so on (the results were shown in online supplemental table S1).

Clinical effect of anti-PD-1/PD-L1 immunotherapy compared with chemotherapy

OS results

OS rates were reported for all the 12 trials, among which one (Reck *et al*¹⁸) reported results of an extension of a previous one (Reck *et al*¹²), which was excluded. The HRs and the 95% CIs of OS for anti-PD-1/PD-L1 immunotherapy compared with chemotherapy were collected

Table 1 Characteristics of the 11 included studies

Author and year	Registered number	Line	Phase of trial	Histology	Phase of stage	Experimental arms	Control arms	Patients (n)	Outcome	PD-L1 expression cut-off
Reck <i>et al</i> ¹²	NCT02142738	First line 3	3	NSCLC	IV	Pembrolizumab	Platinum-based chemotherapy	305	PFS, OS, ORR	None
Mok <i>et al</i> ¹³	NCT02220894	First line 3	3	NSCLC	IV	Pembrolizumab	Platinum-based chemotherapy	1274	OS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 20% PD-L1 $\geq$ 1%
Rittmeyer <i>et al</i> ¹⁴	NCT02008227	Non-first line	3	NSCLC	IIIB or IV	Atezolizumab	Docetaxel	800	OS, PFS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 5% PD-L1 $\geq$ 1% PD-L1 $<$ 1%
Herbst <i>et al</i> ¹⁵	NCT01905657	Non-first line	2/3	NSCLC	IV	Pembrolizumab	Docetaxel	1034	OS, PFS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 1%
Borghaei <i>et al</i> ¹⁶	NCT01673867	Non-first line	3	NSCLC	IIIB or IV	Nivolumab	Docetaxel	582	OS, PFS, ORR	PD-L1 $\geq$ 5% PD-L1 $\geq$ 1% PD-L1 $<$ 1%
Brahmer <i>et al</i> ¹⁷	NCT01642004	Non-first line	3	NSCLC	IIIB or IV	Nivolumab	Docetaxel	272	OS, PFS, ORR	PD-L1 $\geq$ 5% PD-L1 $\geq$ 1% PD-L1 $<$ 1%
Reck <i>et al</i> ¹⁸	NCT02142738	First line 3	3	NSCLC	IV	Pembrolizumab	Platinum-based chemotherapy	305	OS	None
Barlesi <i>et al</i> ¹⁹	NCT02395172	Non-first line	3	NSCLC	IIIB or IV	Avelumab	Docetaxel	792	OS, PFS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 1%
Fehrenbacher <i>et al</i> ²⁰	NCT01903993	Non-first line	2	NSCLC	IV	Atezolizumab	Docetaxel	287	OS, PFS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 5% PD-L1 $\geq$ 1% PD-L1 $<$ 1%
Carbone <i>et al</i> ²¹	NCT02041533	First line 3	3	NSCLC	IV	Nivolumab	Platinum-based chemotherapy	541	PFS, OS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 5%
Rizvi <i>et al</i> ²²	NCT02453282	First line 3	3	NSCLC	IV	Durvalumab	Platinum-based chemotherapy	746	OS, PFS, ORR	PD-L1 $\geq$ 50% PD-L1 $\geq$ 1% PD-L1 $<$ 1%
Wu ²³	NCT02613507	Non-first line	3	NSCLC	IIIB or IV	Nivolumab	Docetaxel	504	OS, PFS, ORR	PD-L1 $\geq$ 1% PD-L1 $<$ 1%

NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; ORR, objective response rate; PD-L1, programmed cell death ligand-1.

Figure 2 Efficacy outcomes of PD-1/PD-L1 immunotherapy versus chemotherapy. (A) Forest plot of HR of OS for anti-PD-1/PD-L1 therapy; (B) forest plot of HR of PFS for anti-PD-1/PD-L1 therapy; (C) forest plot of RR of ORR for anti-PD-1/PD-L1 therapy. All statistical tests were two-sided. ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PFS, progression free survival; RR, risk ratio.

from the remaining 11 trials. A Random-Effects model was selected to perform the meta-analysis because of the significant heterogeneity ($I^2=63\%$). The pooled HR demonstrated that anti-PD-1/PD-L1 immunotherapy was significantly associated with prolonged OS versus chemotherapy (figure 2A, HR=0.78, 95% CI 0.70 to 0.86, $p<0.00001$).

PFS results

Among the 12 trials, 11 studies reported data on PFS. We collected HRs and 95% CIs of PFS for the anti-PD-1/PD-L1 immunotherapy arm versus the chemotherapy group from the 11 studies except for Reck *et al.*¹⁸ A random-effects model was selected because of significant heterogeneity within studies ($I^2=82\%$). The statistical results showed no significant efficacy difference in PFS between anti PD-1/PD-L1 immunotherapy and chemotherapy (figure 2B, HR=0.92, 95% CI 0.80 to 1.05, $p=0.19$).

ORR results

Among the 12 trials, Rizvi *et al.*²² did not report ORR data according to RECIST (version 1.1), and Reck *et al.*¹⁸ only reported the updated OS data and tolerability analysis for Reck *et al.*¹² those two trials were then excluded. A random-effects model was selected for the meta-analysis because of the significant heterogeneity ($I^2=76\%$). The pooled results showed a statistical better clinical

response rate for anti-PD-1/PD-L1 immunotherapy than chemotherapy (figure 2C, RR=1.37, 95% CI 1.08 to 1.74, $p=0.009$).

Safety results

Among the 12 trials, 11 reported treatment-related AEs of any grade and grade 3 or worse except Reck *et al.*¹⁸ The study (Reck *et al.*¹⁸) only reported the updated OS data and tolerability analysis for Reck *et al.*¹² Because of the high heterogeneity ($I^2=49\%$, $p=0.03$; $I^2=82\%$, respectively), random-effects model was selected to do the meta-analysis. The pooled RR results showed significantly lower rates of any grade AEs (online supplemental figure S2A, RR=0.75, 95% CI 0.72 to 0.78, $p<0.00001$) and grade 3 or worse AEs (online supplemental figure S2B, RR=0.31, 95% CI 0.25 to 0.38, $p<0.00001$) in the anti-PD-1/PD-L1 immunotherapy arm than in the chemotherapy arm.

Subgroup analysis by molecular and clinical characteristics for the effect of anti-PD-1/PD-L1 immunotherapy versus chemotherapy

PD-L1 expression level

As shown in Table 1, 10 studies compared the OS and PFS of different PD-L1 expression status except Martin Reck 2016 and Martin Reck 2019.^{12 18} The relevant HRs and 95% CIs of OS and PFS for the anti-PD-1/PD-L1 immunotherapy arm compared with the chemotherapy arm were

collected from relevant studies. Our pooled results illustrated an obvious OS benefit of anti-PD-1/PD-L1 immunotherapy group in PD-L1 $\geq$ 1% population (HR=0.74, 95% CI 0.67 to 0.82, $p<0.00001$, $I^2=39\%$), PD-L1 $\geq$ 5% subgroup (HR=0.63, 95% CI 0.44 to 0.89, $p=0.009$, $I^2=78\%$), PD-L1 $\geq$ 50% subgroup (HR=0.64, 95% CI 0.54 to 0.76, $p<0.00001$, $I^2=47\%$). However, the OS benefit was smaller and not statistically different in the PD-L1 $<$ 1% subgroup (HR=0.85, 95% CI 0.70 to 1.03, $p=0.09$, $I^2=46\%$) (figure 3A). Similarly, PFS benefit was found in PD-L1 $\geq$ 50% subgroup (HR=0.72, 95% CI 0.60 to 0.87, $p=0.0005$, $I^2=54\%$) and PD-L1 $\geq$ 5% subgroup (HR=0.73, 95% CI 0.54 to 1.00, $p=0.05$, $I^2=77\%$). However, for the PD-L1 $\geq$ 1% subgroup (HR=0.89, 95% CI 0.79 to 1.01, $p=0.08$, $I^2=56\%$) and PD-L1 $<$ 1% subgroup (HR=0.99, 95% CI 0.80 to 1.23, $p=0.95$, $I^2=42\%$), the PFS benefit was smaller and not significantly different (figure 3B).

Line of therapy

As shown in table 1, among the 12 selected trials, anti-PD-1/PD-L1 immunotherapy was used in 5 trials as first-line treatment, and 7 trials as non-first-line treatment. A significant OS benefit of anti-PD-1/PD-L1 immunotherapy was observed in the non-first-line treatment population (HR=0.73, 95% CI 0.66 to 0.80, $p<0.00001$, $I^2=29\%$). However, the benefit was smaller and not statistically significant in the first-line treatment subgroup (HR=0.87, 95% CI 0.73 to 1.04, $p=0.12$, $I^2=72\%$). Moreover, no significant PFS benefit was found in both first-line and non-first-line treatment subgroups (HR=0.97, 95% CI 0.74 to 1.28, $p=0.84$, $I^2=89\%$; HR=0.89, 95% CI 0.78 to 1.01, $p=0.07$, $I^2=67\%$, respectively) (online supplemental figure S3).

Histology

Among the 12 trials, 8 trials compared the OS of different LC histologies, and 4 trials reported PFS data. The combined outcomes demonstrated that anti-PD-1/PD-L1 immunotherapy significantly improved OS rates in both squamous and non-squamous subgroups (HR=0.73, 95% CI 0.65 to 0.83, $p<0.0001$, $I^2=0\%$; HR=0.80, 95% CI 0.68 to 0.93, $p=0.005$, $I^2=67\%$, respectively). A significant PFS benefit was observed in squamous population (HR=0.70, 95% CI 0.51 to 0.94, $p=0.02$, $I^2=48\%$), but were not observed in the non-squamous population (HR=0.95, 95% CI 0.68 to 1.33, $p=0.76$, $I^2=87\%$) (online supplemental figure S4).

Age

Among the 12 trials, 8 trials compared the OS of different age subgroups, and 6 trials reported PFS data. The OS benefit of anti-PD-1/PD-L1 immunotherapy was similar in the age $<$ 65 and age $\geq$ 65 subgroups (HR=0.77, 95% CI 0.67 to 0.88, $p=0.0002$, $I^2=52\%$; HR=0.79, 95% CI 0.68 to 0.91, $p=0.001$, $I^2=44\%$, respectively). However, the PFS benefit was smaller and not significantly different between age $<$ 65 and age $\geq$ 65 subgroups (HR=0.85, 95% CI 0.71 to 1.01, $p=0.06$, $I^2=54\%$; HR=0.88, 95% CI 0.69 to

1.14, $p=0.33$, $I^2=70\%$, respectively) (online supplemental figure S5).

Sex

Of the 12 trials, 8 studies compared the OS of different sex subgroup, and 6 reported PFS data. The pooled results illustrated a significant OS benefit both in male and female subgroups (HR=0.75, 95% CI 0.69 to 0.82, $p<0.00001$, $I^2=43\%$; HR=0.82, 95% CI 0.72 to 0.92, $p=0.001$, $I^2=34\%$, respectively). However, PFS benefit was only observed in males (HR=0.73, 95% CI 0.59 to 0.90, $p=0.004$, $I^2=74\%$), and not observed in females (HR=1.09, 95% CI 0.86 to 1.39, $p=0.47$, $I^2=61\%$) (online supplemental figure S6).

Smoking status

Among the 12 trials, 8 trials compared the OS of different smoking status, and 5 trials reported PFS data. OS and PFS benefits of anti-PD-1/PD-L1 immunotherapy were observed in the smoking subgroup (HR=0.77, 95% CI 0.67 to 0.88, $p=0.0001$, $I^2=48\%$; HR=0.79, 95% CI 0.64 to 0.98, $p=0.03$, $I^2=72\%$, respectively). However, no significant OS and PFS benefit were observed in the non-smoking subgroup (HR=0.96, 95% CI 0.76 to 1.22, $p=0.76$, $I^2=25\%$; HR=1.81, 95% CI 1.28 to 2.57, $p=0.0009$, $I^2=13\%$, respectively) (figure 4).

CNS metastasis

Among the 12 trials, 4 trials reported OS data of different CNS metastasis, and 3 trials reported PFS data. The meta-analysis results revealed a statistically significant survival efficacy of anti-PD-1/PD-L1 immunotherapy in the non-CNS metastasis subgroup (HR=0.70, 95% CI 0.62 to 0.78, $p<0.00001$, $I^2=0\%$; HR=0.68, 95% CI 0.47 to 0.97, $p=0.04$, $I^2=83\%$, OS and PFS respectively). Moreover, the OS and PFS efficacy were also existed but not statistically significant in the CNS metastasis subgroup (HR=0.74, 95% CI 0.43 to 1.28, $p=0.29$, $I^2=100\%$; HR=0.74, 95% CI 0.46 to 1.18, $p=0.21$, $I^2=0\%$, respectively) (figure 5).

ECOG performance status

Among the 12 trials, 8 trials reported OS data of different ECOG performance status, and 6 studies showed PFS data. The pooled results showed that significant OS benefit of anti-PD-1/PD-L1 immunotherapy were similar in ECOG 0 and ECOG 1 subgroups (HR=0.76, 95% CI 0.67 to 0.87, $p<0.0001$, $I^2=0\%$; HR=0.75, 95% CI 0.65 to 0.87, $p=0.0001$, $I^2=68\%$, respectively). However, the PFS was longer, but not statistically significant, in the ECOG 0 and ECOG 1 subgroups (HR=0.86, 95% CI 0.61 to 1.21, $p=0.39$, $I^2=79\%$; HR=0.81, 95% CI 0.66 to 1.00, $p=0.05$, $I^2=75\%$, respectively) (online supplemental figure S7).

EGFR mutational status

Among the 12 trials, 3 trials reported OS data of different EGFR mutational status, and 2 trials reported PFS data. Survival efficacy of the anti-PD-1/PD-L1 immunotherapy were observed in EGFR mutant negative

Figure 3 Forest plot for the subgroup analysis of HRs of OS and PFS by PD-L1 expression for PD-1/PD-L1 immunotherapy. (A) OS; (B) PFS. All statistical tests were two-sided. OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

subgroup (HR=0.67, 95% CI 0.59 to 0.76, $p < 0.00001$, $I^2 = 0\%$; HR=0.83, 95% CI 0.73 to 0.94, $p = 0.004$, $I^2 = 0\%$, respectively). However, in EGFR mutant positive

subgroup, there was no OS and PFS benefit (HR=1.12, 95% CI 0.8 to 1.56, $p = 0.51$, $I^2 = 0\%$; HR=1.57, 95% CI 1.06 to 2.32, $p = 0.02$, $I^2 = 0\%$, respectively) (figure 6).

Figure 4 Forest plot for the subgroup analysis of HRs of OS and PFS by smoking status for PD-1/PD-L1 immunotherapy. (A) OS; (B) PFS. All statistical tests were two-sided. OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

KRAS mutational status

Among the 12 trials, 2 reported OS data of different KRAS mutational status subgroups, and only Borghaei *et al*¹⁶ reported PFS data. Accordingly, we only analysed the OS. And the results showed a significant OS benefit of anti-PD-1/PD-L1 immunotherapy in the KRAS-mutant population (HR=0.6, 95% CI 0.39 to 0.93, $p=0.02$, $I^2=0\%$), while the efficacy was smaller and not statistically significant in the KRAS mutation-negative population (HR=0.89, 95% CI 0.68 to 1.16, $p=0.39$, $I^2=0\%$) (figure 7).

Sensitivity analysis

To evaluate the stability and credibility of our findings, we re-analysed the pooled results by removing the studies one by one, analysing the remaining studies. The impact of each study was evaluated on the outcome (except for 'CNS metastasis', 'EGFR mutation status' and 'KRAS mutation status' subgroup analysis, because these subgroups only included 2–3 trials, and leave one trial out could significantly influence the results). The outcomes showed that no single study significantly affected the pooled results.

DISCUSSION

LC has become the most common cancer worldwide, both in terms of incidence and mortality.¹ In recent

years, individualised treatment has become a mainstay of therapy for advanced LC, based on patient and tumour characteristics such as histological type and genotype.²⁴ Biomarkers including EGFR, KRAS, anaplastic lymphoma kinase, B-Raf proto-oncogene, serine/threonine kinase (BRAF) and other driver mutation genes are used for treatment selection in individualised therapy.²⁵ However, these biomarkers are not present in a significant portion of patients that can only resort to cytotoxic chemotherapy, which provides modest survival benefits and a limited safety profile. ICIs targeting the PD-1/PD-L1 axis have propelled the success of immunotherapy for NSCLC, especially in patients with high PD-L1 expression. Besides, other biomarkers, including tumour mutation burden (TMB), microsatellite instability, tumour-infiltrated lymphocyte (TIL), gene expression profiles, can affect the efficacy of ICIs.²⁶ Accordingly, in the present study, we attempted to comprehensively evaluate the clinical efficacy of anti-PD-1/PD-L1 immunotherapy compared with traditional chemotherapy in patients with NSCLC. Further subgroup analysis was performed to investigate the predictive effect of certain molecular and clinical characteristics for anti-PD-1/PD-L1 immunotherapy in advanced NSCLC, which is essential to guide clinical decision-making. By incorporating published data from 12 high-quality RCTs, the present study revealed that

Figure 5 Forest plot for the subgroup analysis of HRs of OS and PFS by CNS metastasis for PD-1/PD-L1 immunotherapy. (A) OS; (B) PFS. All statistical tests were two-sided. CNS, central nervous system; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

anti-PD-1/PD-L1 immunotherapy decreased the hazard for death versus chemotherapy and was also related to higher ORR, lower rate of AEs of any grade and grade

3 or worse AEs in the whole population. In addition, these survival effects persisted in preordained subgroups. Accordingly, the present study confirmed the superiority

Figure 6 Forest plot for the subgroup analysis of HRs of OS and PFS by EGFR mutation status for PD-1/PD-L1 immunotherapy. (A) OS; (B) PFS. All statistical tests were two-sided. EGFR, epidermal growth factor receptor; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

Figure 7 Forest plot for the subgroup analysis of HRs of OS by KRAS mutation status for PD-1/PD-L1 immunotherapy. All statistical tests were two-sided. OS, overall survival; KRAS, Kirsten rat sarcoma viral oncogene homolog; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

of anti-PD-1/PD-L1 immunotherapy for the treatment of NSCLC.

PD-L1 has been recommended as a significant biomarker for the selection of first-line therapy in patients with NSCLC.²⁵ However, much controversy surrounds the role of PD-L1 in predicting the efficiency of anti-PD-1/PD-L1 immunotherapy.²⁷ An earlier study revealed that the OS beneficial of anti-PD-1/PD-L1 immunotherapy was restricted to patients with PD-L1 expression $>1\%$.²⁸ In contrast, another study found the survival benefit of anti-PD-1/PD-L1 immunotherapy in patients with PD-L1 expression $<1\%$.²⁹ Our study illustrated that OS benefit was associated with PD-L1 expression $\geq 50\%$, $\geq 5\%$ and $\geq 1\%$, and PFS benefit was found in patients with PD-L1 expression $\geq 50\%$ and $\geq 5\%$. However, in patients with PD-L1 expression $<1\%$, no statistical OS and PFS benefits were observed. And the results were in line with a previous study.³⁰ Accordingly, PD-L1 expression might be a potential predictor for the efficiency of anti-PD-1/PD-L1 immunotherapy. The above findings suggest a linear relationship between the survival benefit of PD-1/PD-L1 inhibitors and PD-L1 expression, which positively correlated with survival benefit. Furthermore, the latest National Comprehensive Cancer Network guidelines for the NSCLC also emphasised evaluating PD-L1 levels in guiding the anti-PD-1/PD-L1 immunotherapy.³¹ However, the analysis of PD-L1 is influenced by many factors, including sample size, sample location, microenvironmental changes and translational oncology.³² At present, PD-L1 expression can be analysed by immunohistochemistry staining and quantitative PCR analysis; no consensus has been reached regarding which method was the most accurate. Hence, these factors can limit the predictive value of PD-L1 expression; further studies should focus on comparing different methods of quantifying PD-L1 expression and establishing a gold-standard method to provide more accurate values for clinical decision-taking.

ICIs including nivolumab, pembrolizumab and atezolizumab, have been authorised by the FDA to treat patients with NSCLC who failed prior chemotherapy.^{8–10} A significant OS benefit was found in non-first-line ICI treatment populations, and no OS and PFS benefits were observed in the first-line treatment subgroup. These results showed

that consolidation of chemotherapy therapy with anti-PD-1/PD-L1 immunotherapy leads to greater clinical benefits.

Based on the latest WHO classification criteria for LC, NSCLC can be classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, large cell neuroendocrine carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, and other and unclassified carcinoma.³³ Adenocarcinoma is the most prevalent type, accounting for 40%–50%, followed by squamous cell carcinoma at 20%–30% and other types of NSCLC at 10%–20%. Interestingly, different histological types may exhibit different drug therapeutic efficacy due to the differences in gene mutations, RNA transcription and protein expression. Our meta-analysis results showed that patients with squamous cell NSCLC can derive significant clinical benefits from anti-PD-1/PD-L1 immunotherapy in terms of PFS, and these results were consistent with a previous study.³⁴ Interestingly, Dong *et al* documented that EGFR-mutant patients usually have lower expression of PD-L1, lower TMB and lower TIL in patients with EGFR mutations.³⁵ Moreover, non-squamous NSCLC is found in the majority of patients with EGFR mutations. This finding may account for the lower response rate of non-squamous NSCLC to ICIs.

Cancer is regarded as a disease of the elderly, with over 50% of newly diagnosed cases occurring in adults over 65 years.³⁶ Immune senescence is a physiological process, which causes changes in immune function as a result of aging. Immune aging is related to damaged T-cell activation, declined capability of T cells to clear tumour cells, and decreased release of tumour antigens available for processing by antigen-presenting cells.³⁷ Intriguingly, studies found that an age-associated immune dysfunction may affect the efficacy of immunotherapy drugs.³⁸ In our study, greater OS benefit was obtained with anti-PD-1/PD-L1 immunotherapy compared with chemotherapy in patients with NSCLC age <65 and age ≥ 65 , which were in line with a previous meta-analysis.³⁹ However, less survival benefit has been reported with immunotherapy in patients older than 75 years.^{40 41} In the present study, the difference in survival benefits between patients with NSCLC aged less than 75 and aged 75 or older could not

be estimated; thus, our study findings did not reflect the effect of age on the efficiency of ICI treatment. More emphasis should be placed in future studies on patients with NSCLC aged 75 years old or older to properly assess the efficiency of immunotherapy in the elderly population.

The immune response (including the innate and adaptive responses) to exogenous and autoantigens and immune responses differs between males and females. Despite the emerging understanding of sex differences in immune responses in autoimmune diseases and infections, it remains uncertain whether sex-related immune factors influence anti-PD-1/PD-L1 efficiency,⁴² as currently published meta-analyses have reached inconsistent conclusions.^{43 44} The present results illustrated that significant PFS benefit was only observed in the male population, not in the females. Studies have found that in female patients, some tumours have greater ability to evade immune surveillance, which decreases their immunogenicity, substantiating why females are more prone to immunotherapy resistance. In addition, the increased susceptibility to autoimmune diseases in females might explain the higher rate of ICIs-associated AEs, potentially leading to higher rates of treatment discontinuation.⁴⁵ Thus, these factors may explain the dismal effect of anti-PD-1/PD-L1 immunotherapy in female patients.

Smokers account for greater than 80% of all patients with LC, and more than 90% of patients with squamous cell carcinoma are smokers. In this study, anti-PD-1/PD-L1 immunotherapy exhibited clinically significant OS and PFS benefits over chemotherapy in smoking patients, while chemotherapy was associated with a longer PFS in non-smoking patients. Smoking causes ten times more DNA mutations than non-smokers. Champiat *et al* found that somatic mutations in tumour cells could generate neoantigens, which were recognised by T lymphocytes, thus enhancing the therapeutic effect of PD-1/PD-L1 inhibitors.⁴⁶ Moreover, some studies have confirmed that immunotherapy works better for cancers with high numbers of mutated genes.^{47 48} Smoking has also been reported to be positively associated with TMB, which can predict the therapeutic response of ICIs.⁴⁹ The above-mentioned factors may explain why smoking patients experience greater clinical benefits from immunotherapy, prompting us to question whether patients with LC should be encouraged to smoke before immunotherapy? Obviously, the answer is no. As seen in our study, a longer PFS was observed in non-smokers treated with chemotherapy, suggesting that non-smoking patients can also reap benefits from therapy. Second, smoking is a significant risk factor for other diseases such as lung disease and cardiovascular disease and cancer. Third, gene mutations induced by smoking did not occur in a short period but accumulated and slowly evolved over many years. Last but not least, numerous data have shown that smoking cancer patients are more likely to relapse and that treatment can cause various side effects.

CNS metastasis is common in patients with advanced NSCLC, and symptomatic patients tend to have a poorer prognosis.⁵⁰ Since this patient population is often excluded from clinical studies, especially prospective ones, less data is available on the clinical benefit of immunotherapy in CNS metastatic patients.⁵¹ Partially accumulated data on the value of ICIs in this group of patients were observed in prospective exploratory analyses. A phase III OAK study found that patients with CNS metastasis treated with atezolizumab experienced better survival.⁵² Another phase 2 trial demonstrated a significant survival benefit with pembrolizumab in CNS metastatic patients with NSCLC.⁵³ Strikingly, the pooled HR results discovered that anti-PD-1/PD-L1 immunotherapy offered statistically significant OS and PFS benefits in patients with non-CNS metastasis. Due to the lack of relevant research, no accurate conclusion can be drawn. Furthermore, additional experiments are required to verify the predictive effect of CNS metastasis status on the clinical effect of anti-PD-1/PD-L1 immunotherapy.

In the current study, anti-PD-1/PD-L1 immunotherapy showed significant OS and PFS benefits over chemotherapy in EGFR-negative patients. However, a longer PFS was observed in EGFR-positive patients treated with chemotherapy. EGFR is a transmembrane glycoprotein and a member of the ErbB family of tyrosine kinase receptors. EGFR inhibition has been reported to be a key target for cancer chemotherapy.⁵⁴ Dong *et al* found that PD-1 inhibited immunotherapy exhibited poor clinical benefit in EGFR-mutant patients with NSCLC. They also found that EGFR-mutant patients usually had reduced PD-L1 expression, T-cell infiltration and PD-L1⁺/CD8⁺ TIL proportion. What is more, reduced TMB has always been observed in patients with sensitive subtype mutation.³⁵ In addition, an immune-tolerant tumour microenvironment has been found in EGFR-mutant patients with NSCLC.⁵⁵ Therefore, we can conclude that presence of EGFR mutation may be a potential predictor of the clinical effectiveness of PD-1/PD-L1 inhibitors in patients with NSCLC. Nevertheless, different EGFR mutation subtypes have different responses to ICIs in patients with NSCLC,⁵⁶ this might explain why a longer PFS was observed in EGFR mutation positive patients treated with chemotherapy. Therefore, better understanding of the heterogeneity in EGFR mutations may better evaluate the role of EGFR mutations in assessing the efficacy of immunotherapy. Moreover, the design of more prospective studies and RCTs analysing the heterogeneity of EGFR mutation subtypes are required in the future to better understand the value of EGFR mutations in predicting the benefit of ICIs.

Our meta-analysis found anti-PD-1/PD-L1 immunotherapy remarkably improve OS in KRAS-mutant patients compared with those with KRAS wild-type patients. KRAS is an oncogene that has been reported to play a significant role in tumourigenesis.⁴¹ NSCLC tumourigenesis has been reported to be based on the continued expression and signalling of KRAS, making it a high-priority target

Table 2 Summary table of pooled HR for OS and PFS in each subgroup

Subgroup	Pooled HR for OS	Pooled HR for PFS
PD-L1 expression		
PD-L1≥50%	0.64 (0.54 to 0.76)	0.72 (0.60 to 0.87)
PD-L1≥5%	0.63 (0.44 to 0.89)	0.73 (0.54 to 1.00)
PD-L1≥1%	0.74 (0.67 to 0.82)	0.89 (0.79 to 1.01)
PD-L1<1%	0.85 (0.70 to 1.03)	0.99 (0.80 to 1.23)
Line of therapy		
First line	0.87 (0.73 to 1.04)	0.97 (0.74 to 1.28)
Non-first line	0.73 (0.66 to 0.80)	0.89 (0.78 to 1.01)
Histology		
Squamous	0.73 (0.65 to 0.83)	0.70 (0.51 to 0.94)
Non-squamous	0.80 (0.68 to 0.93)	0.95 (0.68 to 1.33)
Age		
<65	0.77 (0.67 to 0.88)	0.85 (0.71 to 1.01)
≥65	0.79 (0.68 to 0.91)	0.88 (0.69 to 1.14)
Sex		
Male	0.75 (0.69 to 0.82)	0.73 (0.59 to 0.90)
Female	0.82 (0.72 to 0.92)	1.09 (0.86 to 1.39)
Smoking status		
Smoking	0.77 (0.67 to 0.88)	0.79 (0.64 to 0.98)
Never smoking	0.96 (0.76 to 1.22)	1.81 (1.28 to 2.57)
CNS metastasis		
CNS metastasis	0.74 (0.43 to 1.28)	0.74 (0.46 to 1.18)
Non-CNS metastasis	0.70 (0.62 to 0.78)	0.68 (0.47 to 0.97)
ECOG performance status		
0	0.76 (0.67 to 0.87)	0.86 (0.61 to 1.21)
1	0.75 (0.65 to 0.87)	0.81 (0.66 to 1.00)
EGFR mutation status		
EGFR mutant positive	1.12 (0.80 to 1.56)	1.57 (1.06 to 2.32)
EGFR mutant negative	0.67 (0.59 to 0.76)	0.83 (0.73 to 0.94)
KRAS mutation status		
KRAS mutant positive	0.60 (0.39 to 0.93)	–
KRAS mutant negative	0.89 (0.68 to 1.16)	

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression free survival.

for the development of future therapeutic drugs. Despite three decades of effort, scientists have not yet succeeded in developing drugs that target KRAS.⁵⁷ D'Incecco *et al*

found that KRAS mutations in NSCLC were positively correlated with PD-L1 expression.⁵⁸ Similarly, Scheel *et al* found that KRAS-mutant patients with NSCLC usually showed a higher PD-L1 expression. Moreover, KRAS mutation has been reported to be closely related to smoking, increased numbers of somatic mutations and expression of neoantigens.⁵⁹ Last but not least, Toki *et al* found that the tumour microenvironment in tumours with KRAS mutations consisted of higher tumour lymphocyte infiltration and infiltrating tumour lymphocytes were basically in an active state.⁶⁰ These explanations indicate that the KRAS mutational status might be a potential predictor of immunotherapy with PD-1/PD-L1. However, given the small number of patients in the KRAS mutation group, this conclusion should be interpreted with caution. More RCTs with larger sample sizes are required to effectively evaluate the predictive effect of KRAS mutation for the efficacy of anti-PD-1/PD-L1 immunotherapy in patients with advanced NSCLC.

In total, this meta-analysis found an improved OS at PD-L1≥1%, ≥5% and ≥50% levels, and a longer PFS at PD-L1≥5% and ≥50% levels. Besides, OS and PFS benefits were observed in non-first line treatment, squamous, male, non-CNS metastasis, smoker, EGFR wild-type and KRAS mutant subgroups. The pooled HRs for OS and PFS within each subgroup were shown in table 2. And our results were partially consistent with a prior meta-analysis.^{41 61} Nonetheless, this study also has some limitations. First, the methods used to quantify PD-L1 were different in the included trials, and this may have a slight impact on PD-L1 expression subgroup analysis. Moreover, HRs and corresponding 95% CIs were directly extracted from the original studies, and no individualised data were used for analysis, which could be a source of reporting bias. Finally, the sample size of some subgroups (CNS metastasis status, EGFR mutation status and KRAS mutational status) was too small and could have influenced the results of our subgroup meta-analysis.

CONCLUSION

In summary, our study demonstrated that anti-PD-1/PD-L1 immunotherapy was linked to a significant increase in OS and ORR, and a lower rate of AEs than chemotherapy. PD-L1 expression, line of therapy, histology, sex, smoking history, CNS metastasis status, EGFR and KRAS mutation status might be potential predictors of the clinical benefits of anti-PD-1/PD-L1 immunotherapy in patients with NSCLC. No differences in treatment efficacy have been found after stratifying for age and ECOG PS score. Accordingly, clinicians can use a combination of these eight factors to select which patients may benefit from PD-1/PD-L1 inhibitors.

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