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ORIGINAL ARTICLE

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Immunotherapy combined with chemotherapy versus chemotherapy alone as the first-line treatment of PD-L1-negative and driver-gene-negative advanced nonsquamous non-small-cell lung cancer: An updated systematic review and meta-analysis

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Abstract

Background: This meta-analysis aimed to compare the efficacy of immunotherapy combined with chemotherapy versus chemotherapy alone as the first-line therapy for patients with programmed death ligand-1 (PD-L1)-negative and driver-gene-negative advanced nonsquamous non-small-cell lung cancer (NSCLC).

Patients and Methods: Eligible randomized trials were identified following the systematic search of PubMed, Cochrane Library, Embase, Web of Science, Wanfang Data, and China Knowledge Resource Integrated Database from January 2000 to June 2022.

Results: Seven trials involving 1132 patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC were included. Immunotherapy combined with chemotherapy showed significantly superior objective response rate (ORR) compared with chemotherapy alone (odds ratio 2.81, 95% confidence interval [CI] 1.69–4.65). Immunotherapy combined with chemotherapy also significantly prolonged the progression-free survival (PFS) (hazard ratio [HR] 0.63, 95% CI 0.55–0.74, $p < 0.001$) and overall survival (OS) (HR 0.68, 95% CI 0.56–0.82, $p < 0.001$) of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC compared to chemotherapy alone. In terms of ≥3 treatment-related adverse events, patients receiving immunotherapy combined with chemotherapy were at higher risk than chemotherapy alone (OR 1.73, 95% CI 1.47–2.05).

Conclusions: This meta-analysis suggested that immunotherapy combined with chemotherapy yielded a better ORR, PFS, and OS, and a higher incidence of treatment-related adverse events as the first-line therapy for patients with PD-L1-negative and driver-gene-negative nonsquamous advanced NSCLC in comparison to chemotherapy alone. A rational treatment protocol should be selected according to the individual condition of the patients.

KEYWORDS
immune checkpoint inhibitor, immunotherapy, meta-analysis, nonsquamous non-small cell lung cancer, programmed death ligand-1

INTRODUCTION

Lung cancer is the malignant tumor with the highest morbidity and mortality in the world, and approximately 85% of patients with lung cancer are non-small-cell lung cancer (NSCLC).[1,2] NSCLC includes squamous NSCLC and nonsquamous NSCLC, among which nonsquamous NSCLC is more common.[3] Almost 70% of NSCLC cases have spread to local or distant sites at the time of diagnosis and are diagnosed with locally advanced or advanced stage due to atypical symptoms in the early stage.[4,5]

For patients with driver-gene-negative advanced nonsquamous NSCLC, chemotherapy has long been the standard treatment option. The approval of immune checkpoint inhibitors has recently provided a key and effective method for the treatment of these patients.[6] A previous meta-analysis showed that programmed death ligand-1 (PD-L1) expression detected via immunohistochemistry was a critical predictive biomarker for predicting the response to immune checkpoint inhibitors in NSCLC.[7] The KEYNOTE-024 trial demonstrated that pembrolizumab monotherapy was more effective than chemotherapy alone in the first-line treatment of PD-L1 expression ≥50% and driver-gene-negative advanced NSCLC.[8] Several studies have also come to this conclusion subsequently and proved that patients with driver-gene-negative advanced NSCLC with PD-L1 expression ≥50% receiving single-agent immunotherapy gained a significantly better survival outcome than those receiving standard chemotherapy.[9–12] Another randomized, open-label, controlled, phase 3 KEYNOTE-042 trial confirmed this result and expanded the benefit population of pembrolizumab monotherapy to PD-L1 expression ≥1%.[13] However, the efficacy of immunotherapy on patients with PD-L1 expression <1% (PD-L1-negative) and driver-gene-negative advanced nonsquamous NSCLC is unclear. In August 2019, a global multicenter retrospective observational study (EXPRESS study) included 2617 patients with stage IIIB/IV NSCLC and the results showed that the proportion of patients with PD-L1 expression <1% was 48%.[14] The EXPRESS II study included 879 Chinese patients with stage IIIB/IV NSCLC, among which the proportion of patients with driver-gene-negative NSCLC was >70%, and the patients with PD-L1 expression <1% accounted for 48.2%.[15] Whether immunotherapy combined with chemotherapy could surpass traditional chemotherapy alone and provide long-term survival and lasting benefits for patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC is still inconclusive and needs to be further explored.

However, no randomized controlled trial (RCT) has directly compared the efficacy and safety profiles of immunotherapy combined with chemotherapy with chemotherapy alone in the first-line treatment for patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC. In this study, we conducted a meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist to comprehensively compare the short- and long-term efficacy of first-line chemoimmunotherapy versus chemotherapy alone in patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC.

MATERIALS AND METHODS

Literature search and selection

A systematic literature search in PubMed, Cochrane Library, Embase, Web of Science, Wanfang Data, and China Knowledge Resource Integrated Database from January 2000 to June 2022 was conducted by two authors independently. The following keywords and their combinations were used for the literature search: "nonsquamous", "non-small-cell lung cancer", "lung neoplasms", "lung carcinoma", "lung cancer", "NSCLC", "lung adenocarcinoma", "ICI", "immune checkpoint blockers", "PD-1 inhibitor", "PD-L1 inhibitor", "immune checkpoint inhibitor", "pembrolizumab", "Keytruda", "nivolumab","Opdivo", "atezolizumab", "atezolizumab", "Tecentriq", "Durvalumab", "Imfinzi", "camrelizumab", "tislelizumab", "sintilimab", "lambrolizumab", "ipilimumab", "tremelimumab", "CTLA 4 Antigen", "Cytotoxic T Lymphocyte Associated Antigen 4", "CTLA-4 Protein", "Cytotoxic T Lymphocyte Antigen 4", "clinical trials", "Randomized clinical trial", and "phase". For the multiple results derived from the same trial, only the latest data were retained.

The inclusion criteria of eligible studies were as follows: (1) previously untreated PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC patients; (2) randomized controlled clinical trials; (3) stage IIIB/IV according to TNM stage (AJCC version 7.0); (4) RCTs comparing an immunotherapy combined therapy to other treatments; and (5) reported hazard ratios (HRs, immunotherapy cohort vs. control) for progression-free survival (PFS) and/or overall survival (OS) stratified by PD-L1 expression. The exclusion criteria were as follows: (1) patients were not treated with immunotherapy or chemotherapy; (2) patients were not treated with first-line treatment; and (3) the study did not provide information on the survival outcomes of patients stratified by PD-L1 expression.

We followed the PRISMA checklist with the extension for meta-analysis.[16] This meta-analysis was registered on the PROSPERO website in July 2022 with the PROSPERO registration number CRD42022348616.

Data extraction and quality assessment

Data extraction and cross-checking were conducted by two authors independently. The following data were then recorded in an Excel sheet: name of the RCT, the research number, trial phase, name of the first author, year of publication, type of study design, study population, the sample size of patients in each group, line of therapy, treatment

regimen, follow-up time, objective response rate (ORR) based on the Response Evaluation Criteria in Solid Tumors (RECIST criteria version 1.0 and 1.1 according to the different publication years), PFS, and OS.

The risks of bias in the included studies were assessed by two authors independently according to the RCT's Cochrane risk of bias assessment: (1) method of generating random sequences; (2) allocation sequence concealment; (3) implementation of blinding; (4) the completion of results; (5) selective reporting assessment; and (6) other biases. These risks of bias were graded as three levels: low risk, high risk, and unclear risk. Any disagreements were resolved by consensus.

Statistical analysis

PFS and OS outcomes were measured by HR with the corresponding 95% confidence interval (95% CI). The ORR was measured using the odds ratios (OR) and the corresponding 95% CI as a measure of association. A 95% CI excluding 1 was considered statistically significant. In terms of PFS and OS, outcomes with HR < 1 would suggest better survival outcomes. ORR outcomes with OR > 1 would suggest better efficacies. Review Manager software (version 5.4.1 for Windows; Cochrane Collaboration, Oxford, UK) was used for all statistical analyses. The χ^2 test and I^2 statistic were used to evaluate statistical heterogeneity. $p > 0.1$ on the χ^2 test or I^2 value <50% was considered to indicate slight heterogeneity, and the fixed-effect model was applied; otherwise, the random-effect model was applied. A p value <0.05 was considered statistically significant.

RESULTS

Eligible studies

A total of 384 trials were assessed for eligibility and seven studies (1132 patients) met our inclusion criteria, of which six were phase 3 studies and one was a phase 2 study. A flowchart of the identification and selection process for this study is shown in Figure 1. The KEYNOTE-021G and KEYNOTE-189 trials compared the clinical benefit achieved in patients in the pembrolizumab + chemotherapy group versus the chemotherapy group.[17,18] The IMPOWER130 and IMPOWER 132 trials compared the clinical benefit achieved in patients in the atezolizumab + chemotherapy group versus the chemotherapy group.[19,20] The CameL, RATIONALE 304, and ORIENT 11 trials compared the efficacy of three PD-1 inhibitors produced in China (carrelizumab, tislelizumab, and sintilizumab) combined with chemotherapy versus chemotherapy in the treatment of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC.[21–23] The baseline characteristics and the outcome measures of the included studies are shown in Table 1. Detailed results of the risk of bias for the enrolled studies are shown in Figure 2. Overall, all seven enrolled studies had a low risk of bias.

ORR

Three trials, including a total of 378 individual patients, 244 of whom underwent immunotherapy and 134 patients underwent chemotherapy, provided ORR data.

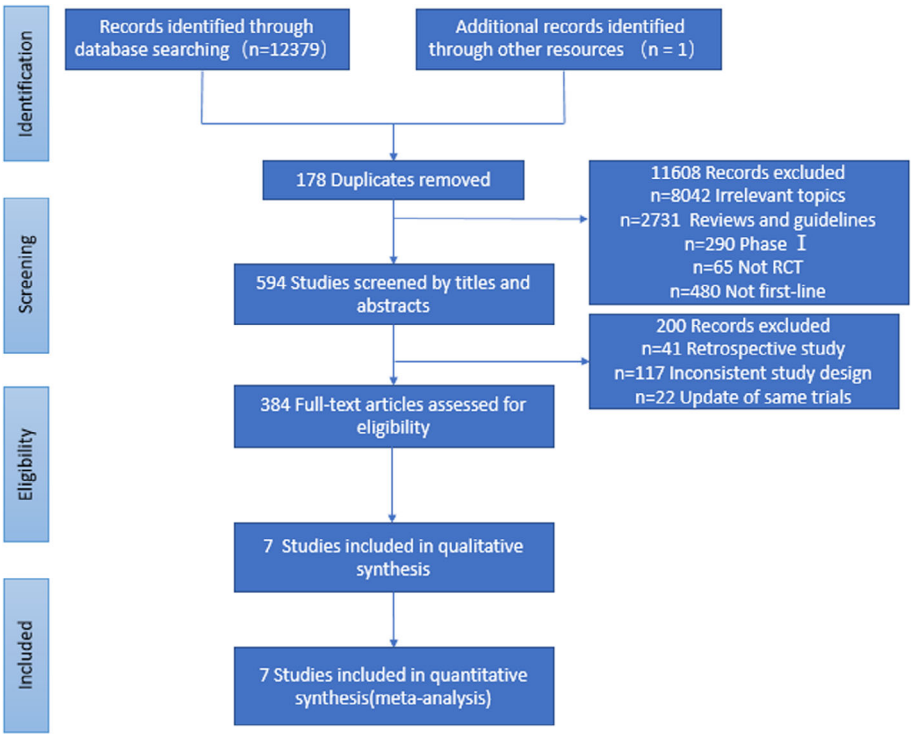
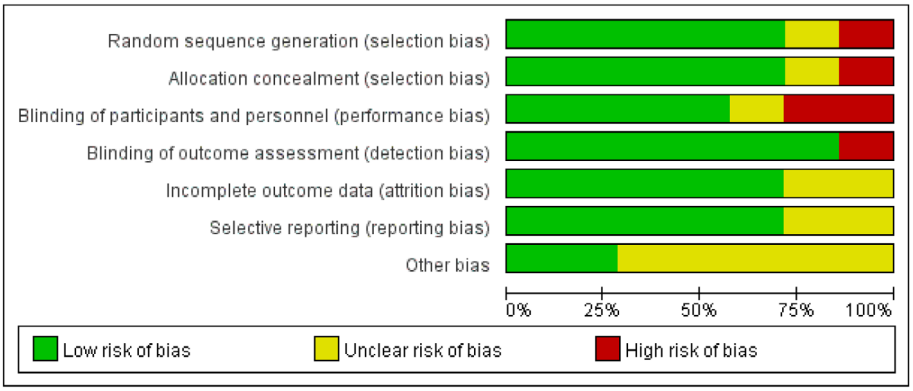


FIGURE 1 Flow-chart of the literature search

TABLE 1 Baseline characteristics of the included randomized controlled trials

	NCT identifier number	Published year	First author	Phase	Arm	Number of patients	HR OS (95% CIs)	HR PFS (95% CIs)	ORR (*n*/*N**)
KEYNOTE-021G	NCT02039674	2016	Langer et al.	II	Pembrolizumab + pembrolizumab + carboplatin	21	0.54 (0.26 to 1.13)	0.35 (0.17 to 0.72)	14/21
					Pembrolizumab + carboplatin	23	–	–	4/23
IMpower130	NCT02367781	2019	West et al.	III	Atezolizumab + nab-paclitaxel + carboplatin	235	0.81 (0.61 to 1.08)	0.72 (0.56 to 0.91)	NA
					Nab-paclitaxel + carboplatin	121	–	–	NA
KEYNOTE-189	NCT02578680	2020	Gadgeel et al.	III	Pembrolizumab + pemetrexed + platinum	127	0.52 (0.36 to 0.74)	0.64 (0.47 to 0.89)	41/127
					Pemetrexed + platinum	63	–	–	9/63
IMpower132	NCT02657434	2021	Nishio et al.	III	Atezolizumab + cisplatin/ carboplatin + pemetrexed	88	NA	0.45 (0.31 to 0.64)	NA
					Cisplatin/carboplatin + pemetrexed	75	–	–	NA
CameL	NCT03134872	2021	Zhou et al.	III	Camrelizumab + pembrolizumab + carboplatin	49	NA	0.76 (0.45 to 1.26)	NA
					Pembrolizumab + carboplatin	69	–	–	NA
RATIONALE 304	NCT03663205	2021	Lu et al.	III	Tislelizumab + chemotherapy	96	NA	0.758(0.469 to 1.224)	40/96
					Chemotherapy	48	–	–	13/48
ORIENT 11	NCT03607539	2021	Yang et al.	III	Sintilimab + pemetrexed + platinum	77	0.75 (0.48–1.19)	–	NA
					Pemetrexed + platinum	40	–	–	NA

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; NA, not available.



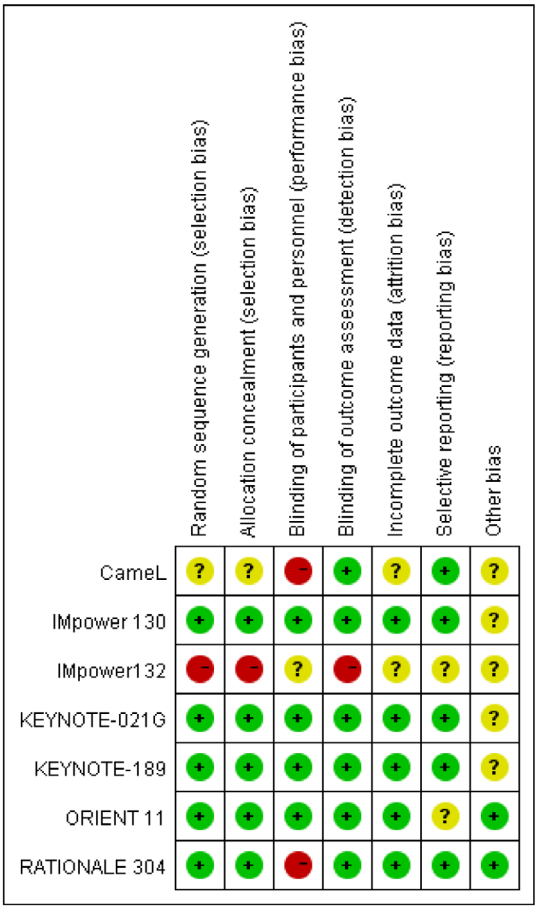


FIGURE 2 Quality assessment: risk of bias according to Cochrane Collaboration's tool. (a) Methodological quality graph: authors' judgment about each methodological quality item presented as percentages across all included studies. (b) Methodological quality summary. Remarks: authors' judgment about each methodological quality item for each included study. +, low risk of bias; ?, unclear risk of bias; −, high risk of bias

For the ORR of first-line therapy, immunotherapy combined with chemotherapy showed significantly superior efficacy compared with chemotherapy alone (OR 2.81, 95% CI 1.69–4.65) (Figure 3a). The analysis was associated with slight heterogeneity (I^2 of 48%), thus a fixed-effect model was applied.

OS and PFS

Six trials, including a total of 1007 individual patients, 616 of whom underwent immunotherapy and 391 of whom underwent chemotherapy, provided PFS data. Four trials, including a total of 707 individual patients, 460 of whom underwent immunotherapy and 247 of whom underwent chemotherapy, provided OS data.

Compared to chemotherapy alone, immunotherapy combined with chemotherapy significantly prolonged the PFS of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC (HR 0.63, 95% CI 0.55–0.74, $p < 0.001$) (Figure 3b). With respect to OS, clinical significance was also achieved (HR 0.68, 95% CI 0.56–0.82, $p < 0.001$) (Figure 3c). Immunotherapy combined with chemotherapy reduced the risk of disease progression by 37% and the risk of death by 32%. The analysis was associated with slight heterogeneity (I^2 of 39% for PFS and I^2 of 0% for OS), thus a fixed-effect model was applied in two analyses.

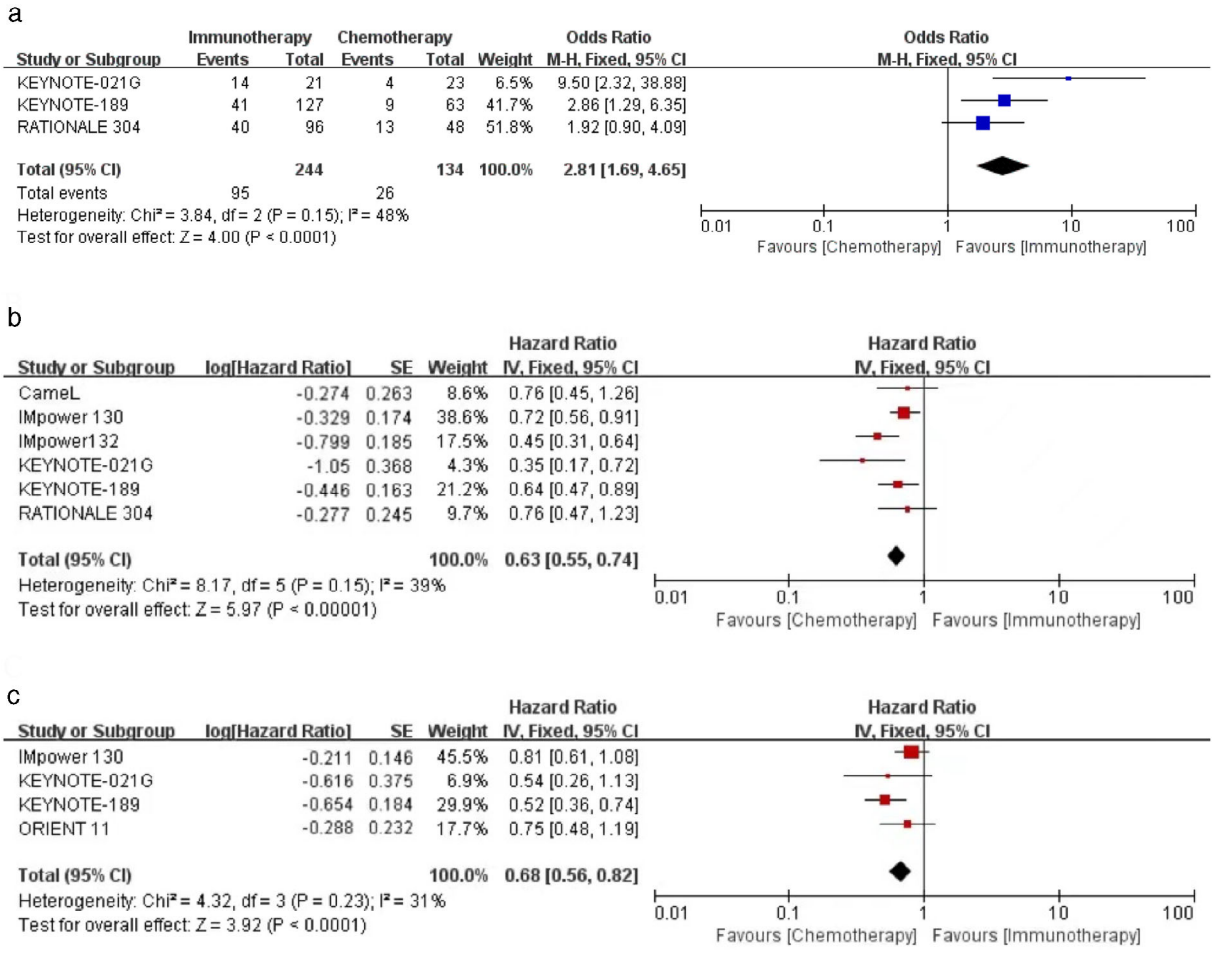


FIGURE 3 Forest plot for ORR (a), PFS (b), and OS (c) of PD-L1-negative and driver-gene-negative nonsquamous NSCLC patients treated with immunotherapy versus chemotherapy. Remarks: outcomes with hazard ratio <1 would suggest better survival outcomes with immunotherapy, while ORR outcomes with odds ratio >1 would suggest better efficacies. NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival

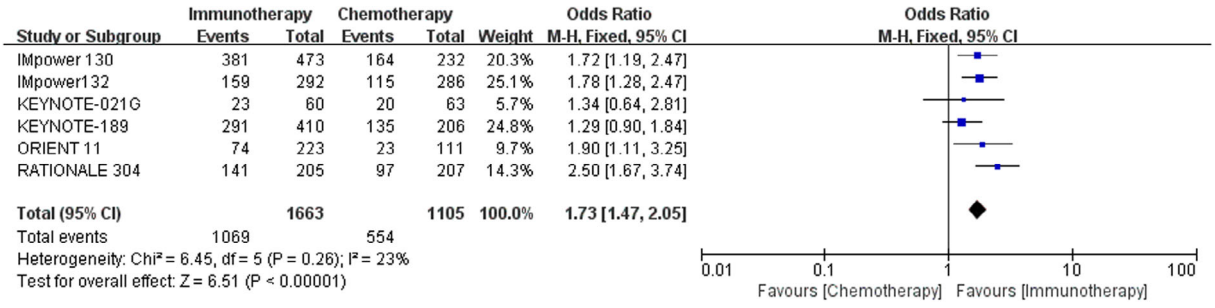


FIGURE 4 Forest plot for ≥3 TRAEs of driver-gene-negative nonsquamous NSCLC patients treated with immunotherapy versus chemotherapy. Remarks: outcomes with odds ratio >1 would suggest higher incidence of adverse events with immunotherapy. NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand-1; TRAEs, treatment-related adverse events

Safety

Data concerning treatment-related adverse events (TRAEs) of involved patients stratified by PD-L1 status were not available, so we compared the safety profiles of patients with driver-gene-negative advanced nonsquamous NSCLC in the two groups. Six trials, including a total of 2768 individual patients, 1663 of whom underwent immunotherapy and 1105 patients who underwent chemotherapy, provided ≥3 TRAEs data. In terms of ≥3 TRAEs, patients receiving immunotherapy combined with chemotherapy were at higher risk than chemotherapy alone (OR 1.73, 95% CI 1.47–2.05) (Figure 4).

The analysis was also associated with slight heterogeneity (I^2 of 23%) and a fixed-effect model was chosen.

DISCUSSION

Recently, there was no large-scale phase 3 RCT to confirm the efficacy of chemoimmunotherapy in patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC. This updated meta-analysis enrolled a total of 1132 previously untreated patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC from seven available RCTs and showed that immunotherapy combined with chemotherapy improved ORR, PFS, and OS compared with chemotherapy alone. Consequently, this study provides a theoretical basis for considering chemoimmunotherapy as a standard of care for patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC.

Theoretically, chemotherapy has been proven to have immunomodulatory properties,[24] therefore immunotherapy in combination with chemotherapy might enhance antitumor immunity and synergistic activity, the biological rationale for which included the recognition of chemotherapy-induced tumor lysis, the release of tumor antigens, and further enhanced immune responses.[24,25] A previous network meta-analysis demonstrated that chemoimmunotherapy could prolong OS in patients with nonsquamous NSCLC compared with chemotherapy alone, but further analysis focusing on the PD-L1-negative subgroup was not performed.[26] Our meta-analysis showed that immunotherapy combined with chemotherapy significantly improved the ORR of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC compared with chemotherapy alone. For PFS, the improvement was statistically significant in immunotherapy in combination with chemotherapy versus chemotherapy in the Keynote-021G, KEYNOTE-189, IMPOWER-130, and IMPOWER-132 trials among the six trials with available data.[17,19,20] In the four trials with available OS data that were enrolled in this meta-analysis, only the Keynote-189 trial showed that pembrolizumab combined with platinum + pemetrexed showed a significant improvement in OS compared with platinum + pemetrexed in the treatment of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC, but the differences between the two treatment modalities were not statistically significant in other trials (KEYNOTE-021G, IMpower130, and ORIENT 11 trials).[17–19,23] The updated data from the KEYNOTE-189 study (23.1-month follow-up time) demonstrated that the median OS (mOS) of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC was 17.2 months in the pembrolizumab + platinum + pemetrexed group versus 10.2 months in the platinum + pemetrexed group (HR 0.52, 95% CI 0.36–0.74); the median PFS (mPFS) was 6.2 months and 5.1 months, respectively (HR 0.64, 95% CI 0.47–0.89).[18] In addition, pembrolizumab combined with platinum + pemetrexed significantly improved the PFS-2 of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC compared with chemotherapy alone (mPFS2 12.6 vs. 8.9 months, HR 0.46, 95% CI 0.33–0.66), which suggests that the clinical benefit of pembrolizumab plus chemotherapy was maintained in subsequent-line therapy. It is still noteworthy that the HR of PFS-2 (0.46) was lower than that of PFS-1 (0.64), which supports the preferential use of pembrolizumab in combination with chemotherapy as the first-line therapy in patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC.[18]

In terms of safety, immunotherapy-related adverse events (irAEs) could affect nearly all organs and tissues of the body and mainly develop in the skin, gastrointestinal tract, endocrine system, respiratory system, nervous system, muscles, and joints.[27] The chemotherapy-related adverse events (crAEs) were mainly bone marrow suppression and gastrointestinal reactions. A previous network meta-analysis showed that immunotherapy combined with chemotherapy showed significantly higher incidences of grade 3–5 TRAEs than chemotherapy alone in patients with driver-gene-negative advanced nonsquamous NSCLC (risk ratios (RR), 1.24, 95% CI 1.00–1.54).[26] The Keynote-021G and Keynote-189 trials showed that patients treated with pembrolizumab + chemotherapy and chemotherapy alone showed similar incidences of grade 3–5 TRAEs in patients with driver-gene-negative advanced nonsquamous NSCLC (38.3% vs. 31.7%, $p = 0.444$; 71.0% vs. 65.5%, $p = 0.618$). The RATIONALE 304 trial showed that patients with driver-gene-negative advanced nonsquamous NSCLC treated with tislelizumab + chemotherapy experienced higher incidences of grade 3–5 TRAEs than those treated with chemotherapy alone (68.8% vs. 46.9%, $p < 0.001$). Since there were no RCTs disclosing the difference in the incidence of TRAEs between immunotherapy combined with chemotherapy and chemotherapy alone in the PD-L1-negative subgroup, we compared the safety profiles of patients with driver-gene-negative advanced nonsquamous NSCLC in the two groups in this meta-analysis. In terms of ≥3 TRAEs, patients receiving immunotherapy combined with chemotherapy were at higher risk than chemotherapy alone (OR 1.73, 95% CI 1.47–2.05), which was consistent with the outcomes from the previous study.[26] The above results indicated that immunotherapy combined with chemotherapy could not only improve the short-term efficacy and help to quickly control the development of the disease but also improve the long-term survival outcomes of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC. TRAEs varied among different chemoimmunotherapy regimens. Among the various chemoimmunotherapy regimens, the pembrolizumab combined with platinum + pemetrexed is the preferred regimen, with relatively high efficacy and tolerable toxicities at present.

Currently, in addition to immune checkpoint inhibitors in combination with chemotherapy, dual immune checkpoint inhibitors, anti-angiogenetic drugs in combination with chemotherapy, and chemotherapy alone are also optional treatment modalities for patients with PD-

L1-negative and driver-gene-negative advanced nonsquamous NSCLC. The Checkmate 227 part 1A trial showed that the combination of nivolumab and ipilimumab ($n = 278$) achieved a more favorable ORR (37.1% vs. 32.6%), PFS (HR 0.83, 95% CI 0.68–1.01), and OS (HR 0.81, 95% CI 0.67–0.99) in patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC in contrast to chemotherapy alone ($n = 279$).[28] Anti-angiogenetic drugs in combination with chemotherapy yielded limited survival benefits in patients with driver-gene-negative advanced nonsquamous NSCLC. Only ECOG 4599 and BEYOND phase 3 trials showed that OS was significantly improved with bevacizumab in combination with chemotherapy compared to chemotherapy alone in the treatment of patients with treatment-naive driver-gene-negative advanced nonsquamous NSCLC (mOS 12.3 vs. 10.3 months, HR 0.79, 95% CI 0.67–0.92, $p = 0.003$; mOS 20.3 vs. 13.8 months, HR 0.57, 95% CI 0.36–0.89), while other trials did not obtain positive results.[29–34] Due to limited data in earlier anti-angiogenetic drug-containing RCTs, we did not perform a subgroup analysis stratified by PD-L1 expression to discriminate patients who would benefit most from anti-angiogenetic drugs in combination with chemotherapy.[29–35] Dual immunotherapy could be considered for patients who could not tolerate chemotherapy alone; anti-angiogenic therapy combined with chemotherapy could be considered for patients with contraindications to immunotherapy. RCTs focused on comparing the efficacy of immune checkpoint inhibitors in combination with chemotherapy with other treatment modalities, such as anti-angiogenetic drugs in combination with chemotherapy and dual immunotherapy in the treatment of patients with PD-L1-negative and driver-gene-negative advanced nonsquamous NSCLC, are warranted.

There were several limitations of this meta-analysis. First, because there were no RCTs focusing on patients with PD-L1-negative NSCLC, clinical data on patients with PD-L1-negative NSCLC were derived from subgroup analyses of each RCT with a relatively low grade of evidence. Second, differences in PD-L1 assay methods in different studies may affect the overall analysis results. Prospective RCTs focused on the first-line treatment for patients with PD-L1-negative NSCLC are warranted in the future.

CONCLUSION

In conclusion, this meta-analysis suggested that immunotherapy combined with chemotherapy yielded a better ORR, PFS, and OS and a higher incidence of ≥3 TRAEs as the first-line therapy for patients with PD-L1-negative and driver-gene-negative nonsquamous advanced NSCLC in comparison to chemotherapy alone. A rational treatment protocol should be selected according to the individual condition of the patients. Among the various chemoimmunotherapy regimens, the pembrolizumab combined with a platinum + pemetrexed regimen was chosen in preference.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets developed and analyzed during this study are available from the corresponding author on reasonable request.

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