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

Yue Chai | Xinyu Wu | Yifeng Zou | Xue Zhang | Hua Bai | Mei Dong | Jianchun Duan

CAMS Key Laboratory of Translational Research on Lung Cancer, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence
Jianchun Duan, CAMS Key Laboratory of Translational Research on Lung Cancer, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
Email: duanjianchun79@163.com

Funding information
National Science Foundation of China (NSFC), Grant/Award Number: 81971236; CSCO-Cinda Tumor Immunotherapy Research Fund (2019) Project, Grant/Award Number: Y XD2019-215

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 \(\geq 50\%\) 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 \(\geq 50\%\) 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 \(\geq 1\%\).\(^13\) 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 $\chi^2$ test and $I^2$ statistic were used to evaluate statistical heterogeneity. $p > 0.1$ on the $\chi^2$ 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.
| 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          | 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 |
| IMpower130            | 2019           | West et al.   | III   | Pembrolizumab + carboplatin + nab-paclitaxel + carboplatin | 23 | – | – | 4/23 |
| KEYNOTE-189           | 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 |
| IMpower132            | 2021           | Nishio et al. | III   | Atezolizumab + cisplatin/carboplatin + pemetrexed | 88 | NA | 0.45 (0.31 to 0.64) | NA |
| CameL                 | 2021           | Zhou et al.   | III   | Camrelizumab + pembrolizumab + carboplatin | 49 | NA | 0.76 (0.45 to 1.26) | NA |
| RATIONALE 304         | 2021           | Lu et al.     | III   | Tislelizumab + chemotherapy | 96 | NA | 0.758 (0.469 to 1.224) | 40/96 |
| ORIENT 11             | 2021           | Yang et al.   | III   | Sintilimab + pemetrexed + platinum | 77 | 0.75 (0.48–1.19) | – | NA |

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

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. 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). 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. 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). 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.

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. Dual immunotherapy could be considered for patients who could not tolerate chemotherapy alone; anti-angiogenetic 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.

ACKNOWLEDGMENTS

This study was supported by the National Science Foundation of China (NSFC) (grant number 8197112364) and CSCO-Cinda Tumor Immunotherapy Research Fund (2019) Project (grant number Y-YD2019-215).

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.

ORCID

jianchun Duan https://orcid.org/0000-0003-1479-2304

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7.
3. Snee M, Cheeseman S, Thompson M, et al. Treatment patterns and survival outcomes for patients with non-small cell lung cancer in the UK in the preimmunotherapy era: a REAL-oncology database analysis from the I-O optimise initiative. BMJ Open. 2021;11:e6396.
4. Jin X, Guan Y, Zhang Z, Wang H. Microarray data analysis on gene and miRNA expression to identify biomarkers in non-small cell lung cancer. BMC Cancer. 2020;20:329.
5. Yang ZY, Liu L, Mao C, et al. Chemotherapy with cetuximab versus chemotherapy alone for chemotherapy-naive non-small cell lung cancer. Cochrane Database Syst Rev. 2014;17:D9948.
6. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, et al. NCCN guidelines insights: non-small cell lung cancer, Version 2.2021. J Natl Compr Canc Netw. 2021;19:254.
7. Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. Transl Lung Cancer Res. 2019;8:413–28.
8. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: Pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. J Clin Oncol. 2019;37:537–46.
9. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Goëss T, Fülöp A, et al. Five-year outcomes with Pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥50. J Clin Oncol. 2019;37:2339–49.
10. Mok T, Wu YL, Budak I, et al. Pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥50. J Clin Oncol. 2021;39:2339–49.
11. Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. N Engl J Med. 2020;383:1328–39.
12. Sezer A, Kilickap S, Gümüş M, Bondarenko I, Özgüroğlu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a
multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet. 2021;397:592–604.

13. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, de Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378:2078–92.

14. Dietel M, Savelov N, Salanova R, Micke P, Bigras G, Hida T, et al. Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: the global, multicenter EXPRESS study. Lung Cancer. 2019;134:174–9.

15. Lin D, Yang X, Jiang L, Wang W, Hou Y, Li Y, et al. Real-world prevalence of PD-L1 expression in Chinese patients with advanced or metastatic NSCLC: Express II study. J Thorac Oncol. 2021;16:S410.

16. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

17. Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JCH, Powell SF, et al. Long-term overall survival from KEYNOTE-021 cohort G: Pemetrexed and carboplatin with or without Pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. J Thorac Oncol. 2021;16:162–8.

18. Gadgeel S, Rodriguez-Abreu D, Speranza G, Esteban E, Felip E, Domíne M, et al. Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus Pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol. 2020;38:1505–17.

19. West H, McClod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:924–37.

20. Nishio M, Barlesi F, West H, Ball S, Bordoni R, Cobo M, et al. Atezolizumab plus chemotherapy for first-line treatment of nonsquamous NSCLC: results from the randomized phase 3 IMpower132 trial. J Thorac Oncol. 2021;16:653–64.

21. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CamEL): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med. 2021;9:305–14.

22. Zhou C, Wu L, Fan Y, Wang Z, Liu L, Chen G, et al. Sintilimab plus platinum and gemcitabine as first-line treatment for advanced or metastatic squamous NSCLC: results from a randomized, double-blind, phase 3 trial (ORIENT-12). J Thorac Oncol. 2021;16:1501–11.

23. Yang Y, Wang Z, Fang J, Yu Q, Han B, Cang S, et al. Final overall survival (OS) data of sintilimab plus pemetrexed (SPP) and platinum as first-line (1L) treatment for locally advanced or metastatic nonsquamous NSCLC (AMsnqNSCLC) in the phase III ORIENT-11 study. Ann Oncol. 2022;33:S28.

24. Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ. 2014;21:15–25.

25. Rosner S, Forde PM. Chemotherapy + PD-1/PD-L1 blockade should be the preferred option in the neoadjuvant therapy of NSCLC. J Thorac Oncol. 2022;17:503–9.

26. Chai Y, Wu X, Bai H, Duan J. Combined immunotherapy with chemotherapy versus bevacizumab with chemotherapy in first-line treatment of driver-gene-negative non-squamous non-small cell lung cancer: an updated systematic review and network meta-analysis. J Clin Med. 2022;11:1655.

27. Hussain S, Chehade R, Boldt RG, Raphael J, Blanchette P, Maleki Vareki S, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors—a systematic review and meta-analysis. Cancer Treat Rev. 2021;92:102134.

28. Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-line Nivolumab plus Ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. J Thorac Oncol. 2022;17:289–308.

29. Sandler A, Gray R, Perry MC, Brahamer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542–50.

30. Zhou C, Wu YL, Chen G, Liu X, Zhu Y, Lu S, et al. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. J Clin Oncol. 2015;33:2197–204.

31. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAIL). Ann Oncol. 2010;21:1804–9.

32. Leighl NB, Zatloukal P, Mezger J, Ramlau R, Moore N, Reck M, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAIL). J Thorac Oncol. 2010;5:1970–6.

33. Niño S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced nonsquamous non-small-cell lung cancer. Lung Cancer. 2012;76:362–7.

34. Zinner RG, Obasaju CK, Spiegel DR, Weaver RW, Reck FT, Waterhouse DM, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol. 2015;10:1344–42.

35. Galetta D, Cinieri S, Picconti S, Gebbia V, Morabito A, Borsellino N, et al. Cisplatin/Pemetrexed followed by maintenance Pemetrexed versus carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in advanced nonsquamous lung cancer: the GOIM (Gruppo Oncologico Italia Meridionale) ERACLE phase III randomized trial. Clin Lung Cancer. 2015;16:262–73.