Comparative efficacy and safety of first-line PD-1/PD-L1 inhibitors in immunotherapy for non-small cell lung cancer: A network meta-analysis

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Abstract. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. The emergence of programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors offers new therapeutic options for patients with advanced NSCLC, but a comprehensive evaluation of their efficacy and safety is still lacking. In the present study randomized controlled trials (RCTs) published from January 2005 to May 2023 were identified through searches of PubMed, the Cochrane Library and Embase. Analysis focused on 10 PD-1/PD-L1 inhibitors for stages III and IV NSCLC in studies evaluating overall survival (OS), progression-free survival (PFS), the objective response rate, the disease control rate (DCR) and the incidence of severe treatment-related and immune-related adverse events. A total of 37 RCTs involving 31,779 patients were included in the analysis. Compared with chemotherapy, tislelizumab, pembrolizumab and nivolumab all significantly improved OS, with tislelizumab showing the highest probability of being the best treatment for improving OS and DCR. While cemiplimab and tislelizumab had the highest probabilities of improved PFS, no significant differences were observed across all PD-1/PD-L1 inhibitors. Combination therapies, such as nivolumab or cemiplimab with chemotherapy, increased OS and PFS but also increased the incidence of severe treatment-related adverse events. In particular, cemiplimab and pembrolizumab were associated with a greater risk of severe immune-related adverse events. In conclusion, PD-1/PD-L1 inhibitors, especially tislelizumab, pembrolizumab and nivolumab, were effective first-line treatments for NSCLC, providing survival benefits. However, the combination of PD-1/PD-L1 inhibitors with chemotherapy increased the risk of severe adverse events. Further research is needed to optimize treatment strategies.

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Introduction

Lung cancer is a common malignant tumor, with non-small cell lung cancer (NSCLC) accounting for 80-85% of lung cancer cases. The morbidity and mortality rates associated with lung cancer are significantly higher than those of other cancer types worldwide. The latest statistics indicate that 609,820 individuals in the United States died from cancer in 2023, 127,070 of whom died from lung cancer (1,2).

The traditional treatments for NSCLC mainly include chemotherapy, surgical resection and radiotherapy. However, chemotherapy can provide only moderate benefits with limited safety, and as such immune checkpoint inhibitors (ICIs) that have been introduced in recent years have become the primary treatment method (3). In particular, ICIs targeting programmed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1) enhance antitumor effects by restoring the function of suppressed effector T cells and producing durable responses in a number of patients with metastatic and advanced NSCLC (4). To date, a total of 10 PD-1/PD-L1 inhibitors have been approved to treat NSCLC in China and the United States. Among them, camrelizumab, sugemalimab and sintilimab are listed only in China, whereas cemiplimab is listed only in the United States. Nivolumab, pembrolizumab, atezolizumab, durvalumab, tislelizumab and toripalimab are all available in both the United States and China. With the exception of durvalumab, sugemalimab and atezolizumab, which are PD-L1 inhibitors, the remaining seven are PD-1 inhibitors.

Although previous network meta-analyses (NMAs) have examined the efficacy and safety of PD-1/PD-L1 inhibitors in the treatment of advanced NSCLC, these studies typically

included a limited number of drugs, most of which were Food and Drug Administration (FDA)-approved. By contrast, the present study aimed to expand the scope by including a broader range of PD-1/PD-L1 inhibitors that are approved for first-line treatment of advanced NSCLC, providing a more comprehensive evaluation of available therapies. Moreover, a broader range of outcome measures were assessed in the present study, offering a more comprehensive evaluation of both efficacy and safety. Thus, the present meta-analysis provides a more complete and updated perspective, which may offer valuable insights for selecting the most appropriate PD-1/PD-L1 inhibitor in the first-line treatment of advanced NSCLC.

Materials and methods

The present NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement.

Search strategies. The PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/) and Embase (www.embase.com/) databases were searched for all randomized controlled trials (RCTs) on the treatment of NSCLC with PD-1/PD-L1 inhibitors from January 1, 2005 to May 31, 2023. The search consisted of three domains: Intervention (PD-1/PD-L1 inhibitors or individual drugs), patients with NSCLC and RCTs (Table SI).

Selection criteria. RCTs were included if they met the following criteria: i) Studies based on phase III RCTs; ii) patients with NSCLC (stage III or IV) confirmed either histologically or cytologically; iii) patients who received a PD-1/PD-L1 inhibitor (sintilimab, tislelizumab, camrelizumab, nivolumab, pembrolizumab, atezolizumab, sugemalimab, durvalumab, cemiplimab or toripalimab); iv) patients with long-term assessment data, including overall survival (OS) and progression-free survival (PFS), short-term assessment data, including the objective response rate (ORR) and the disease control rate (DCR), and safety outcomes based on the incidence of grade ≥3 treatment-related adverse events (TRAEs) or grade ≥3 immune-related adverse events (irAEs); v) RCTs with a sample size in a single group (sum of all dose groups) >50; and vi) the study had been published and was written in the English language. Studies that did not meet these criteria and those that shared the same dataset were excluded. In cases where more than two articles were published for the same clinical trial, the most recent data for each outcome were obtained from each article.

Literature screening and data extraction. In total, two authors independently conducted the literature screening and data extraction, with verification by the third author. The extracted data included the basic characteristics of the study, such as the first author and publication year, median follow-up time, experiment type and stage, pathological type, number of included cases, median age, sex, intervention measures, smoking status, Eastern Cooperative Oncology Group performance status score, liver metastasis and brain metastasis. The extracted clinical outcome data included the most recent OS and PFS rates, 95% confidence intervals (CIs) of the hazard ratios (HRs), ORRs, DCRs and the incidences of ≥3 TRAEs and ≥3 irAEs.

Risk of bias and certainty of evidence assessment. In total, two authors independently assessed the risk of bias in eligible studies via the revised Cochrane Collaboration Risk of Bias 2 (RoB 2.0) tool for RCTs (5). Any discrepancies were resolved through consensus with a third author. All endpoints from the five domains were assessed, and the overall risk of bias was rated as 'low risk', 'some concerns' or 'high risk'. RoB 2.0 includes five modules to assess the risk of bias in RCTs, each containing multiple signal questions. The possible answers are 'Yes (Y)', 'Probably Yes (PY)', 'Probably No (PN)', 'No (N)' and 'No Information (NI)'. In some cases, 'Not Applicable (NA)' may also be used. Each module is evaluated independently to determine the overall risk of bias. If all five modules are rated as low risk, the overall risk is considered low. If none of the modules are high risk but some raise concerns, the overall risk is categorized as 'some concerns'. If any module is assessed as high risk, or multiple modules show potential risks with significant impact, the overall risk is deemed high. This entire process is based on a qualitative evaluation of the signal issues in each module, without using quantitative ratings or thresholds to define 'low risk', 'some concerns' or 'high risk'.

Statistical analysis. In the study, HRs with 95% CIs were used as the effect sizes for OS and PFS rates, and ORs with 95% CIs were used as the effect sizes for ORRs, DCRs, ≥3 TRAEs and ≥3 irAEs. Bayesian network meta-analysis was conducted using a random effects model via R software (version 4.2.2; https://www.R-project.org/) and the gemtc package (version 1.0; cran.r-project.org/package=gemtc). The result was 4 chains with 100,000 iterations per chain and 10,000 burn-in iterations (with an interval of 10). R software was also used to identify the probability of each treatment being the optimal ranking for the 10 endpoints, and the surface under the cumulative ranking curve (SUCRA) was presented in the ranking graph. An I^2 test was employed to assess statistical heterogeneity. An I^2 value ≤50% indicated minimal heterogeneity, whereas values >50% suggested significant heterogeneity. Subgroup analyses were conducted to identify the origins of heterogeneity and explore the factors associated with clinical advantages.

Results

Study selection. A total of 7,109 articles were identified through the initial database search, with 1,208 from PubMed, 2,713 from Embase and 3,188 from the Cochrane Library. After 2,138 duplicate records were removed, 4,971 articles were screened. The initial search results and selection process are detailed in Fig. 1. Ultimately, 37 RCTs (including 31,935 patients) were included in the systematic review, including 3 that reported extended follow-up (further publications of the patient follow-up) (6-8).

Characteristics of the included studies. Among the 37 RCTs analyzed, 13 (including 15,758 patients) included comparisons of an intervention group receiving PD-1/PD-L1 inhibitor monotherapy and a control group receiving chemotherapy (9-21). Additionally, 13 RCTs (including 8,668 patients) included comparisons of an intervention group treated with PD-1/PD-L1 inhibitor monotherapy and a control group administered a placebo (periodic combination chemotherapy) (7,8,22-32).

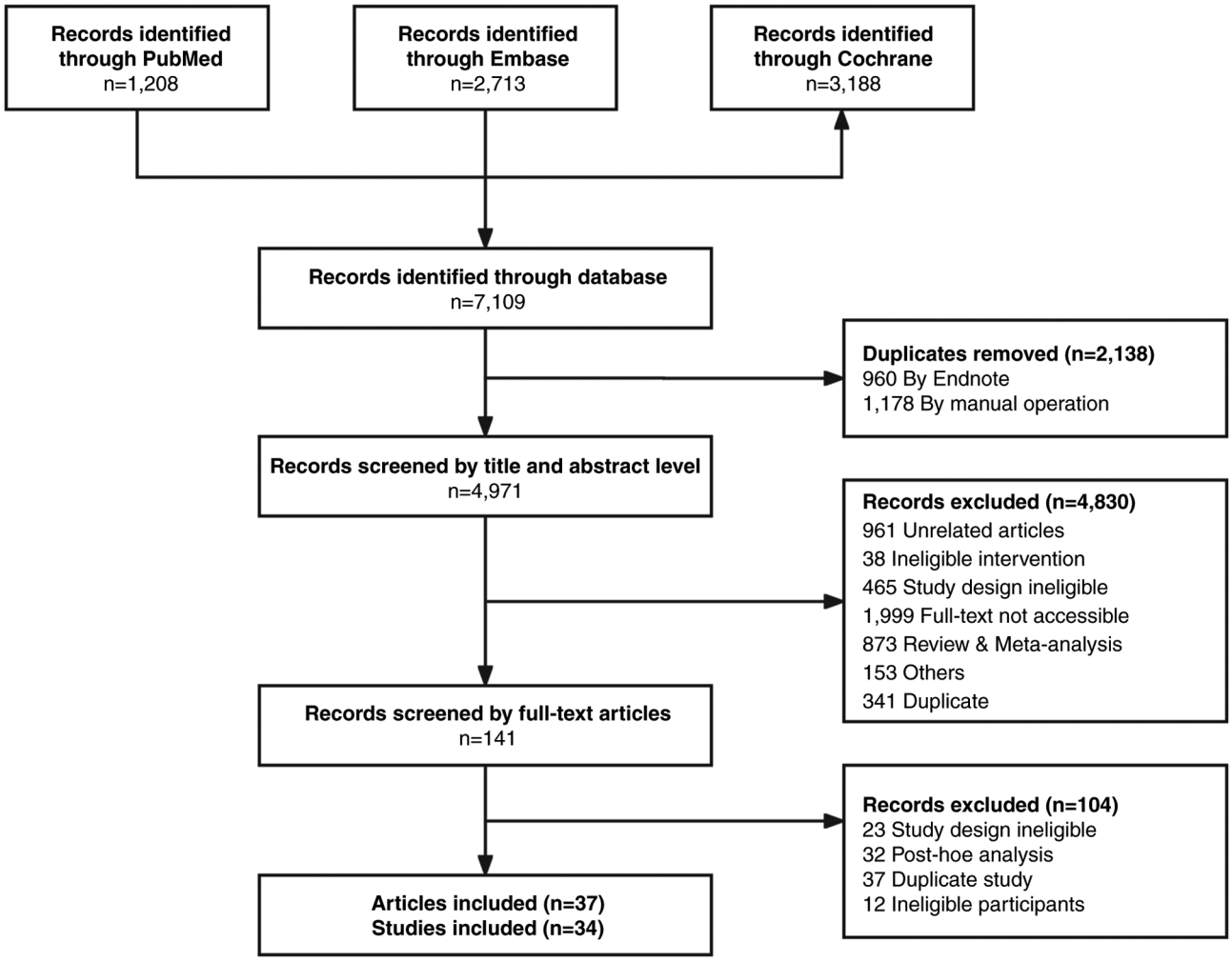


Figure 1. Flow chart of study selection. The flow chart outlines the process of study selection, including the number of records identified, screened and excluded. In total, two independent reviewers screened the titles, abstracts and full texts of the identified articles for eligibility, following the predefined inclusion criteria. The chart provides a visual summary of the total number of studies included in the final analysis after each stage of screening.

Furthermore, 11 RCTs (including 7,509 patients) compared an intervention group treated with PD-1/PD-L1 inhibitors combined with chemotherapy with a control group receiving chemotherapy only (6,33-42). The characteristics of the RCTs are listed in Table SII.

Assessment of the risk of bias. The risk of bias assessment results for OS, PFS, ORR, DCR, grades ≥3 TRAEs and grades ≥3 irAEs are outlined in Table SIII, with 23, 22, 15, 15, 24 and 13 studies rated as high risk for each indicator. These high-risk studies were still included in the analyses to ensure a comprehensive evaluation of the available evidence. This approach was taken to avoid potential bias from selective exclusion and to provide a balanced representation of the data.

Comparisons of OS, PFS, ORR and DCR. The NMA included an intervention group treated with PD-1/PD-L1 inhibitor monotherapy and a control group treated with chemotherapy, an intervention group treated with PD-1/PD-L1 inhibitors combined with chemotherapy and a control group treated with chemotherapy only, and an intervention group treated with PD-1/PD-L1 inhibitor monotherapy and a control group treated with placebo. The OS and PFS network plots are depicted in Fig. 2A and B, respectively.

The NMA of the PD-1/PD-L1 inhibitors vs. chemotherapy model included 13 RCTs (9-21) (Figs. S1A, S2A, S3A, S4A, S5A and S6A). In terms of OS, there were 4,674 patients in the intervention group receiving PD-1/PD-L1 inhibitor monotherapy and 4,091 patients in the chemotherapy group. Tislelizumab (HR, 0.66; 95% CI, 0.44-0.98), pembrolizumab (HR, 0.72; 95% CI, 0.59-0.88) and nivolumab (HR, 0.76; 95% CI, 0.61-0.94) showed significant advantages over chemotherapy (Fig. 3). Tislelizumab had the highest probability (43%) of ranking as the best treatment (Table SIV). Toripalimab and tislelizumab had the highest SUCRA values for OS (0.93 and 0.78, respectively; Table SV). Patients receiving PD-1/PD-L1 inhibitors did not demonstrate significantly greater benefits in terms of PFS than patients receiving standard chemotherapy (Fig. 3). Notably, while no significant differences were observed, cemiplimab had the highest probability (49%) of being ranked as the most effective treatment (Table SIV). Both cemiplimab and tislelizumab were the top contenders for improving PFS, with respective SUCRA values of 0.80 and 0.74 (Table SV). In terms of both the ORR and DCR, tislelizumab had the highest probability of being ranked as the

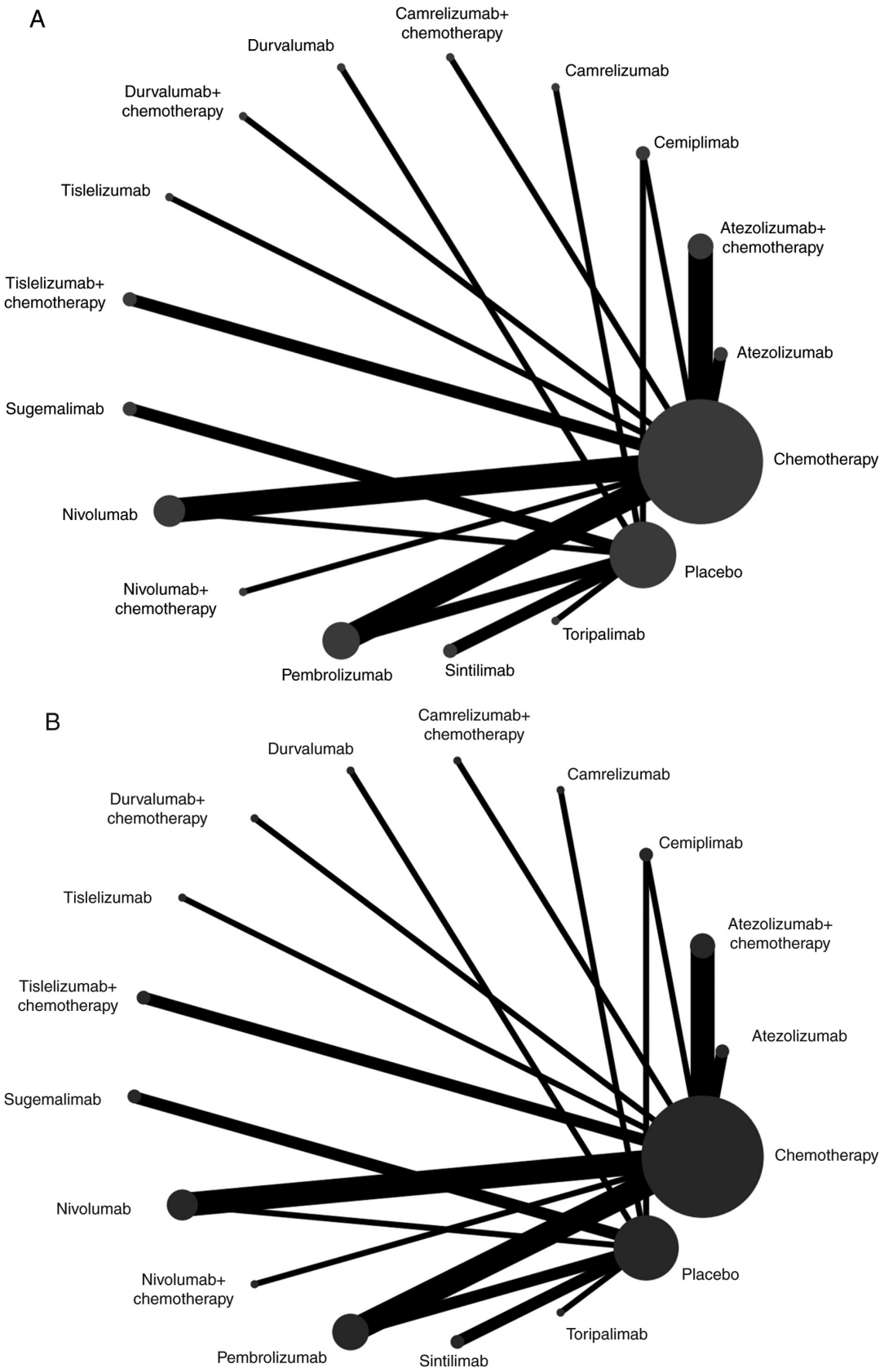


Figure 2. Network plots of eligible comparisons for long-term outcomes. The sizes of the nodes reflect the number of trials that investigated each specific treatment. Treatments that were directly compared are connected by lines, with the thickness of these lines indicating the number of trials that evaluated that particular comparison. (A) The OS network of eligible comparisons. This plot illustrates the direct and indirect comparisons among various treatments for NSCLC, focusing on OS as the primary outcome. Chemotherapy is the largest node, signifying that it has been the most frequently compared treatment in the included studies. The plot helps visualize which treatments have been compared head-to-head and which are linked through indirect evidence. (B) The PFS network of eligible comparisons. This plot shows the network of treatments compared in terms of PFS in NSCLC. Like in the OS network, chemotherapy is the largest node, reflecting its extensive evaluation against other therapies. The connections between treatments provide insights into both direct and indirect comparisons made across the included trials. OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung cancer.

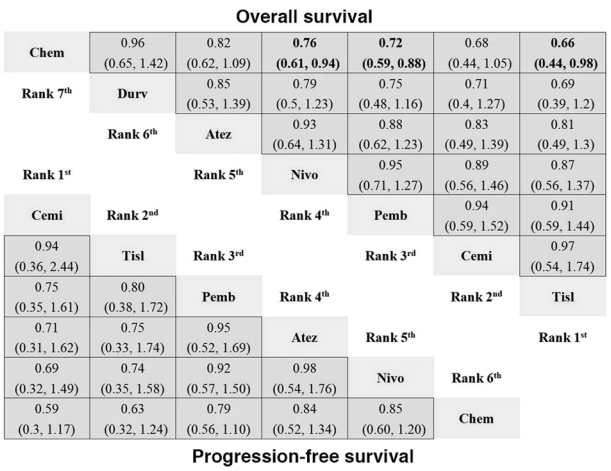


Figure 3. Network meta-analysis for OS and PFS of PD-1/PD-L1 inhibitors vs. chemotherapy. The analysis presents the HR with 95% confidence interval for each treatment, showing the ranking and relative efficacy of PD-1/PD-L1 inhibitors compared with chemotherapy. For comparisons of the OS (right upper half) and PFS (left lower half), a HR <1 favors the column defining treatment. Significant differences are show in bold in the figure. Chem, chemotherapy; Durv, durvalumab; Atez, atezolizumab; Nivo, nivolumab; Pemb, pembrolizumab; Cemi, cemiplimab; Tisl, tislelizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

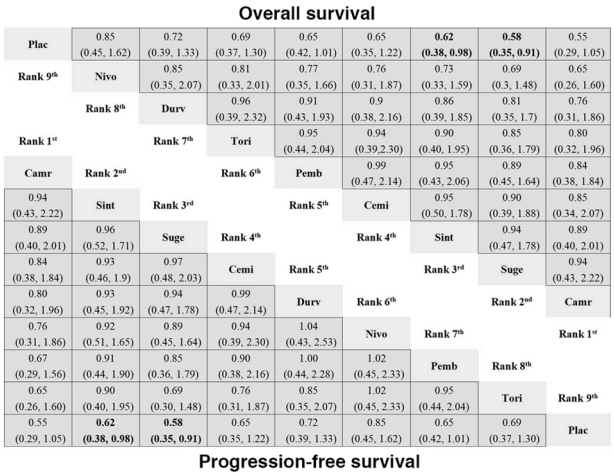


Figure 4. Network meta-analysis for OS and PFS of PD-1/PD-L1 inhibitors vs. placebo. The analysis presents HR with 95% confidence interval for each treatment, showing the ranking and relative efficacy of PD-1/PD-L1 inhibitors compared with placebo. For comparisons of the OS (right upper half) and PFS (left lower half), a HR <1 favors the column defining treatment. Significant differences are boldly shown in the figure. Plac, placebo; Durv, durvalumab; Atez, atezolizumab; Nivo, nivolumab; Pemb, pembrolizumab; Cemi, cemiplimab; Tisl, tislelizumab; Tori, toripalimab; Sint, sintilimab; Suge, sugemalimab; Camr, camrelizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

best treatment, with probabilities of 61 and 75%, respectively (Table SIV).

The NMA of the PD-1/PD-L1 inhibitor vs. placebo model included 13 RCTs (7,8,22-32) (Figs. S1B, S2B, S3B, S4B, S5B and S6B). In terms of OS, the intervention group comprised 3,264 patients receiving PD-1/PD-L1 inhibitor monotherapy or a PD-1/PD-L1 inhibitor in combination with chemotherapy, whereas the control group included 1,999 patients receiving a placebo (Table SIV). In terms of OS and PFS, both sugemalimab and sintilimab significantly outperformed the placebo (Fig. 4). Camrelizumab and sugemalimab ranked the best for OS, with SUCRA values of 0.76 and 0.72, respectively (Table SV), whereas camrelizumab and sintilimab ranked the best for PFS, with SUCRA values of 0.91 and 0.61, respectively (Table SV). In terms of ORR, camrelizumab (vs. placebo) still led, with a 30% probability of being the most effective (Table SIV), whereas for DCR, sintilimab (vs. placebo) maintained a 36% probability of ranking as the best treatment (Table SV).

The NMA of the PD-1/PD-L1 inhibitors with chemotherapy vs. chemotherapy model included 11 RCTs (6,33-42) (Figs. S1C, S2C, S3C, S4C, S5C and S6C). The intervention group receiving PD-1/PD-L1 inhibitors in combination with chemotherapy consisted of 2,728 patients, whereas the chemotherapy-only group comprised 2,372 patients. Nivolumab (HR, 0.57; 95% CI, 0.35-0.93) or cemiplimab (HR, 0.83; 95% CI, 0.71-0.98) in combination with chemotherapy demonstrated a significant advantage over chemotherapy alone in terms of the OS metric (Fig. 5). Compared with chemotherapy, nivolumab + chemotherapy consistently had a higher probability (77%) of being ranked as the best treatment (Table SIV). Nivolumab + chemotherapy and camrelizumab + chemotherapy ranked the best for OS, with SUCRA values of 0.91 and 0.70, respectively (Table SV). With respect to PFS, PD-1/PD-L1 inhibitors + chemotherapy consistently resulted in an improved PFS than

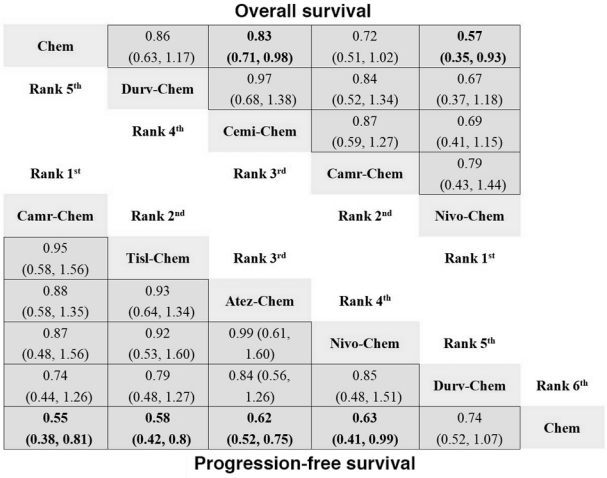


Figure 5. Network meta-analysis for OS and PFS of PD-1/PD-L1 inhibitors + chemotherapy vs. chemotherapy. The analysis presents HR with 95% confidence interval for each treatment, showing the ranking and relative efficacy of PD-1/PD-L1 inhibitors + chemotherapy compared with chemotherapy. For comparisons of the OS (right upper half) and PFS (left lower half), a HR <1 favors the column defining treatment. Significant differences are boldly shown in the figure. Chem, chemotherapy; Dur-Chem, durvalumab + chemotherapy; Cemi-Chem, cemiplimab + chemotherapy; Cam-Chem, camrelizumab + chemotherapy; Niv-Chem, nivolumab + chemotherapy; Tis-Chem, tislelizumab + chemotherapy; Ate-Chem, atezolizumab + chemotherapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

standard chemotherapy monotherapy, with the only exception being durvalumab + chemotherapy (Fig. 5). Camrelizumab + chemotherapy had the highest probability (46%) of being ranked as the best treatment (Table SIV). Camrelizumab + chemotherapy and tislelizumab + chemotherapy ranked as the best

treatments for PFS, with SUCRA values of 0.80 and 0.71, respectively (Table SV). For the ORR and DCR, camrelizumab + chemotherapy had the highest probability of being ranked as the best treatment, with probabilities of 45 and 55%, respectively (Table SIV).

Safety. The NMA comparing PD-1/PD-L1 inhibitors with chemotherapy revealed that cases of grade ≥3 TRAEs were identified in 12 RCTs (9-18,20,21), whereas instances of grade ≥3 irAEs were noted in 8 RCTs (9,10,12-15,20,21). With respect to grade ≥3 TRAEs, all PD-1/PD-L1 inhibitor groups, except for durvalumab (OR, 0.79; 95% CI, 0.68-2.30), showed a reduction in severe TRAEs (Fig. S5A). Chemotherapy was associated with a greater incidence of grade ≥3 TRAEs, with a SUCRA value of 0.94 (Table SV). In terms of grade ≥3 irAEs, cemiplimab (OR, 19.00; 95% CI, 1.10-9.9x10^2) and pembrolizumab (OR,8.40; 95% CI, 2.80-41.00) were more susceptible to severe irAEs (Fig. S6A), ranking poorly with SUCRA values of 0.79 and 0.62, respectively (Table SV).

Compared with placebo (22-24,27-32), no significant differences were found for grade ≥3 TRAEs (Fig. S5B). However, sugemalimab (OR, 21.00; 95% CI, 2.60-6.80x10^2), nivolumab (OR, 10.00; 95% CI, 1.40-72.00) and pembrolizumab (OR, 3.90; 95% CI, 1.00-16.00) were more likely to result in severe irAEs (22-25,27-32) (Fig. S6B), with sugemalimab having the highest SUCRA value of 0.88 (Table SV).

When combination therapies (PD-1/PD-L1 inhibitors + chemotherapy) were compared with chemotherapy alone (6,33-42), cemiplimab (OR, 1.60; 95% CI, 1.30-2.00), camrelizumab (OR, 2.60; 95% CI, 1.50-4.30) and tislelizumab (OR, 1.80; 95% CI, 1.20-2.90) in combination with chemotherapy were associated with increased grade ≥3 TRAEs (Fig. S5C). Camrelizumab and tislelizumab combinations had high SUCRA values of 0.96 and 0.80 for severe TRAEs, respectively (Table SV). Both combinations were also linked to higher incidences of grade ≥3 irAEs (36-41) (Fig. S6C), with SUCRA values of 0.79 and 0.69, respectively (Table SV).

Subgroup analysis according to the tumor histology characteristics. The 32 RCTs included information on tumor histology characteristics. Among them, 27 RCTs exclusively included patients with non-squamous NSCLC, whereas 20 RCTs specifically focused on patients with squamous NSCLC (Table SII). In the analysis of direct comparisons of OS in patients with non-squamous NSCLC, all experimental treatments demonstrated superior outcomes compared with chemotherapy (Fig. 6). Toripalimab exhibited the most significant improvement in OS (HR, 0.48; 95% CI, 0.31-0.75). In the indirect comparisons, toripalimab showed superior OS benefits over atezolizumab (HR, 0.59; 95% CI, 0.37-0.94) and nivolumab (HR, 0.57; 95% CI, 0.36-0.92), whereas sintilimab exhibited greater OS benefits over nivolumab (HR, 0.74; 95% CI, 0.56-0.98). In the analysis of direct comparisons for PFS in patients with non-squamous NSCLC, toripalimab, sintilimab, pembrolizumab, cemiplimab, durvalumab and atezolizumab demonstrated a significant advantage over chemotherapy (Fig. 6).

In the subgroup of patients with squamous NSCLC, treatments were administered to 3,383 patients, whereas 2,693 patients were in the control arms (Table SII). In the analysis of direct comparisons of OS in patients with squamous NSCLC, the cemiplimab, camrelizumab, tislelizumab and nivolumab experimental treatments were associated with a greater OS than chemotherapy (Fig. 7). According to the results of the indirect comparison analysis, cemiplimab outperformed atezolizumab, toripalimab and durvalumab. Camrelizumab was superior to toripalimab and atezolizumab. In addition, both sintilimab and pembrolizumab were superior to toripalimab (Fig. 7). For PFS in patients with squamous NSCLC, toripalimab, sintilimab, pembrolizumab, cemiplimab, durvalumab and atezolizumab all demonstrated superiority over chemotherapy (Fig. 7).

Discussion

The landscape of cancer immunotherapy has significantly evolved with the introduction of PD-1/PD-L1 inhibitors, offering novel avenues for enhancing patient survival and delaying disease progression. As each PD-1/PD-L1 inhibitor has distinct advantages, the present study aimed to evaluate the efficacy and safety profiles of 10 PD-1/PD-L1 inhibitors that have been approved by the FDA and the National Medical Products Administration for the treatment of NSCLC.

Several previous NMAs have evaluated first-line PD-1/PD-L1 inhibitors for NSCLC (43-45), but the present study offers a more comprehensive and updated synthesis. Unlike the study by Wang *et al* (43), which recommends therapies based on PD-L1 status and only considered grade 3 or higher TRAEs for the safety assessment, the present study evaluated both efficacy and safety profiles. Additionally, the analysis by Wang *et al* was limited to only four drugs and found pembrolizumab combined with chemotherapy the most effective for the general cohort. The results of the present study highlighted tislelizumab, pembrolizumab and nivolumab as demonstrating significant advantages over conventional chemotherapy in improving OS. Jiang *et al* (44) assessed only five inhibitors with a focus on OS and TRAEs, suggesting cemiplimab as having a favorable risk-benefit profile but noting limitations due to short follow-up data. By contrast, the present study provides a more robust evaluation by incorporating longer follow-up data and considering a broader range of outcomes, including OS, PFS, ORR, DCR and both TRAEs and irAEs, for 10 approved PD-1/PD-L1 inhibitors. In terms of efficacy, the present study also highlights cemiplimab and tislelizumab for their notable benefits in PFS. Li *et al* (45) focused exclusively on combination therapies with chemotherapy for extensive-stage small-cell lung cancer (ES-SCLC) and similarly noted that treatment with serplulimab plus chemotherapy was the superior modality. However, the present study focused on NSCLC and went beyond combination therapies, encompassing monotherapies and other combination options. The results of the present study indicated that, when combined with chemotherapy, nivolumab and cemiplimab achieved notable improvements in OS compared with chemotherapy alone.

The findings from a study based on summarized subgroup data and studies with similar, though not identical, inclusion criteria suggested that ethnic differences did not significantly affect response rates or survival outcomes in patients with NSCLC receiving immunotherapy with nivolumab,

Overall survival

Chem	0.84 (0.73, 0.97)	**0.82 (0.71, 0.95)**	**0.73 (0.58, 0.91)**	**0.72 (0.55, 0.95)**	**0.72 (0.52, 0.99)**	**0.72 (0.62, 0.83)**	**0.63 (0.49, 0.80)**	**0.60 (0.43, 0.83)**	**0.48 (0.31, 0.75)**
Rank 10th	**Nivo**	0.98 (0.79, 1.20)	0.86 (0.65, 1.13)	0.86 (0.63, 1.17)	0.86 (0.60, 1.21)	0.85 (0.69, 1.04)	**0.74 (0.56, 0.98)**	0.71 (0.50, 1.02)	**0.57 (0.36, 0.92)**
	Rank 9th	**Atez**	0.88 (0.67, 1.15)	0.88 (0.65, 1.20)	0.88 (0.62, 1.24)	0.87 (0.71, 1.07)	0.76 (0.57, 1.01)	0.73 (0.51, 1.04)	**0.59 (0.37, 0.94)**
Rank 1st		**Rank 8th**	**Dur**	0.99 (0.70, 1.43)	0.99 (0.67, 1.48)	0.99 (0.70, 1.41)	0.86 (0.62, 1.21)	0.83 (0.53, 1.31)	0.66 (0.4, 1.1)
Tori	**Rank 2nd**		**Rank 7th**	**Cemi**	1.00 (0.65, 1.52)	0.99 (0.73, 1.35)	0.87 (0.58, 1.30)	0.83 (0.54, 1.27)	0.67 (0.39, 1.16)
0.98 (0.37, 2.60)	**Sint**	**Rank 3rd**		**Rank 6th**	**Camr**	0.99 (0.76, 1.30)	0.87 (0.60, 1.25)	0.83 (0.56, 1.23)	0.67 (0.4, 1.13)
0.96 (0.37, 2.50)	0.98 (0.38, 2.52)	**Pemb**	**Rank 4th**		**Rank 5th**	**Pemb**	0.87 (0.66, 1.16)	0.84 (0.59, 1.19)	0.67 (0.42, 1.08)
0.87 (0.33, 2.30)	0.89 (0.34, 2.32)	0.91 (0.36, 2.32)	**Camr**	**Rank 5th**		**Rank 4th**	**Sint**	0.96 (0.64, 1.44)	0.77 (0.47, 1.29)
0.81 (0.35, 1.90)	0.83 (0.36, 1.92)	0.85 (0.37, 1.91)	0.93 (0.40, 2.13)	**Cemi**	**Rank 6th**		**Rank 3rd**	**Tisl**	0.8 (0.46, 1.41)
0.78 (0.34, 1.84)	0.80 (0.35, 1.85)	0.82 (0.36, 1.84)	0.90 (0.39, 2.05)	0.96 (0.49, 1.91)	**Durv**	**Rank 7th**		**Rank 2nd**	**Tori**
0.75 (0.34, 1.66)	0.77 (0.35, 1.67)	0.78 (0.37, 1.66)	0.86 (0.40, 1.86)	0.92 (0.50, 1.71)	0.96 (0.52, 1.76)	**Atez**	**Rank 8th**		**Rank 1st**
0.75 (0.27, 2.02)	0.76 (0.31, 1.77)	0.78 (0.29, 2.04)	0.85 (0.35, 1.99)	0.92 (0.39, 2.16)	0.95 (0.45, 1.92)	0.99 (0.51, 1.89)	**Tisl**	**Rank 9th**	
0.74 (0.30, 1.78)	0.76 (0.29, 2.05)	0.77 (0.33, 1.78)	0.85 (0.32, 2.27)	0.91 (0.44, 1.86)	0.95 (0.40, 2.24)	0.99 (0.44, 2.23)	0.99 (0.40, 2.40)	**Suge**	**Rank 10th**
0.62 (0.29, 1.34)	0.63 (0.31, 1.35)	0.64 (0.32, 1.34)	0.71 (0.34, 1.50)	0.76 (0.43, 1.36)	0.79 (0.45, 1.40)	0.82 (0.51, 1.36)	0.83 (0.39, 1.82)	0.84 (0.46, 1.59)	**Nivo**
0.48 (0.24, 0.97)	**0.49 (0.25, 0.97)**	**0.50 (0.26, 0.96)**	0.55 (0.28, 1.08)	**0.59 (0.36, 0.96)**	**0.61 (0.38, 0.98)**	**0.64 (0.44, 0.94)**	0.65 (0.32, 1.31)	0.65 (0.38, 1.12)	0.78 (0.56, 1.04)

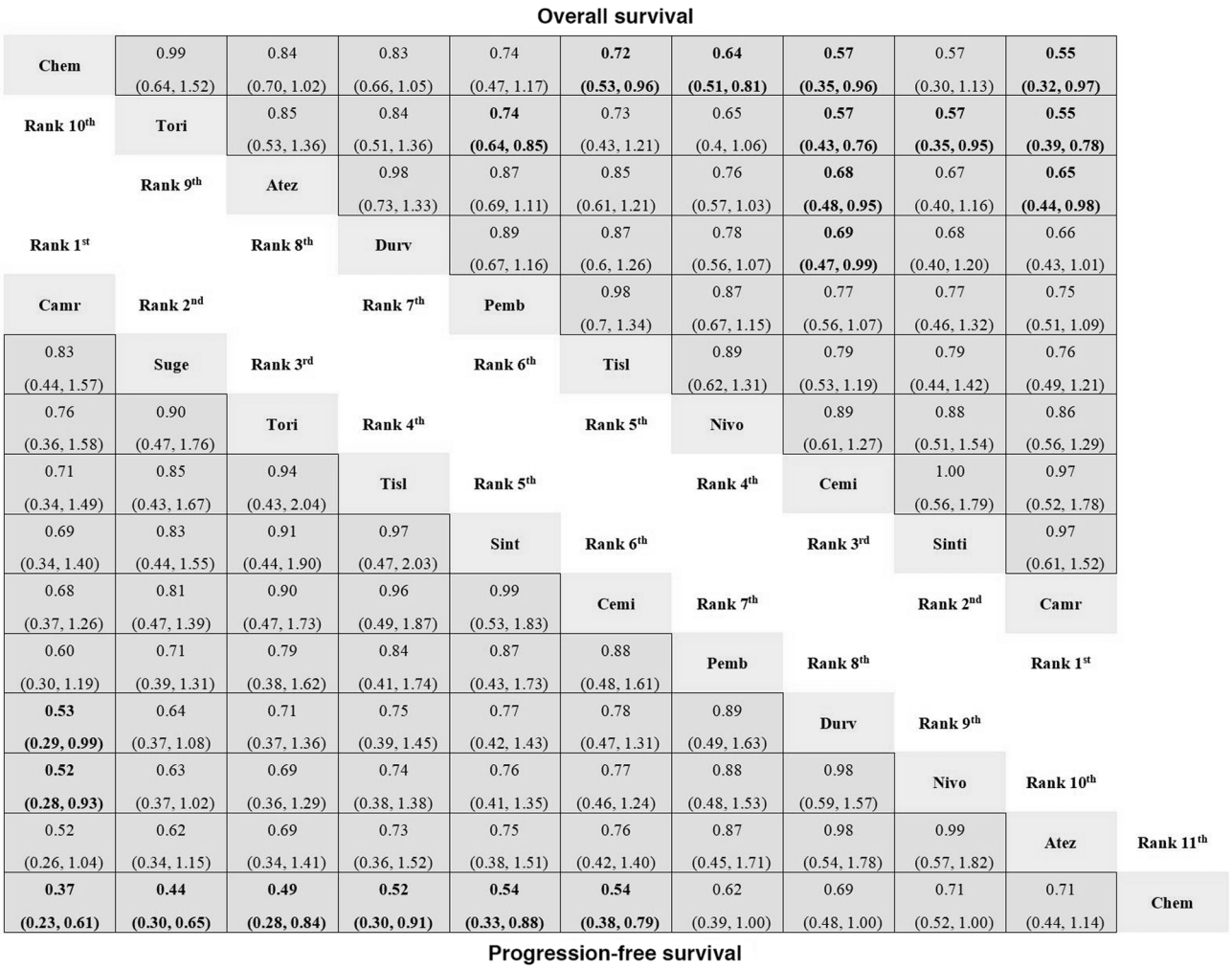
Rank 11th | **Chemo**

Progression-free survival

Figure 6. Network meta-analysis for OS and PFS of patients with non-squamous NSCLC. HR with 95% confidence interval are presented for various treatment regimens, including PD-1/PD-L1 inhibitors and chemotherapy. Both direct and indirect comparison results for patients with non-squamous NSCLC are illustrated, showing the comparative efficacy of each therapy in extending OS and PFS. For comparisons of the OS (right upper half) and PFS (left lower half), a HR <1 favors the column defining treatment. Significant differences are boldly shown in the figure. Chem, chemotherapy; Durv, durvalumab; Atez, atezolizumab; Nivo, nivolumab; Pemb, pembrolizumab; Cemi, cemiplimab; Tisl, tislelizumab; Tori, toripalimab; Sint, sintilimab; Suge, sugemalimab; Camr, camrelizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer.

pembrolizumab, atezolizumab or durvalumab (46). Further analyses on ethnic differences in treatment responses to PD-1/PD-L1 inhibitors, including nivolumab, pembrolizumab and atezolizumab, in real-world settings have shown variable outcomes across ethic groups. Specifically, African-American patients with advanced NSCLC treated with these agents experienced longer times to treatment discontinuation and OS compared with White patients, suggesting that a lower occurrence of hyperprogressive disease may contribute to these favorable outcomes (47). While efficacy differences in survival outcomes across ethnic groups appear limited, previous research has indicated that the characteristics of AEs in Asian cancer populations using PD-1/PD-L1 inhibitors differed from those observed in Western patients. For example, in Asian patients, camrelizumab has been linked to a high rate of reactive capillary hemangiomas, a side effect that has not been reported among Western patients (48). In addition, the results of the present study further indicated that camrelizumab combined with chemotherapy was more likely to result in severe TRAEs. Similarly, a retrospective review of patients with stage IV solid tumors treated with PD-1/PD-L1 inhibitors at MedStar Georgetown Cancer Institute between 2013 and 2018 found a significantly higher incidence of irAEs in Caucasian patients (60.4%) than in African-American patients (30.8%) (49).

Tislelizumab, China's first independently developed PD-1 inhibitor, was launched in December 2019 and received approvals in Europe and the United States in 2023 and 2024, respectively. Regulatory approval in China has facilitated its widespread use in clinical practice. A study indicated that the combination of tislelizumab with chemotherapy was not a cost-effective first-line treatment option for



Chem	0.99 (0.64, 1.52)	0.84 (0.70, 1.02)	0.83 (0.66, 1.05)	0.74 (0.47, 1.17)	**0.72 (0.53, 0.96)**	**0.64 (0.51, 0.81)**	**0.57 (0.35, 0.96)**	0.57 (0.30, 1.13)	**0.55 (0.32, 0.97)**
Rank 10th	**Tori**	0.85 (0.53, 1.36)	0.84 (0.51, 1.36)	**0.74 (0.64, 0.85)**	0.73 (0.43, 1.21)	0.65 (0.4, 1.06)	**0.57 (0.43, 0.76)**	**0.57 (0.35, 0.95)**	**0.55 (0.39, 0.78)**
	Rank 9th	**Atez**	0.98 (0.73, 1.33)	0.87 (0.69, 1.11)	0.85 (0.61, 1.21)	0.76 (0.57, 1.03)	**0.68 (0.48, 0.95)**	0.67 (0.40, 1.16)	**0.65 (0.44, 0.98)**
Rank 1st		**Rank 8th**	**Durv**	0.89 (0.67, 1.16)	0.87 (0.6, 1.26)	0.78 (0.56, 1.07)	**0.69 (0.47, 0.99)**	0.68 (0.40, 1.20)	0.66 (0.43, 1.01)
Camr	**Rank 2nd**		**Rank 7th**	**Pemb**	0.98 (0.7, 1.34)	0.87 (0.67, 1.15)	0.77 (0.56, 1.07)	0.77 (0.46, 1.32)	0.75 (0.51, 1.09)
0.83 (0.44, 1.57)	**Suge**	**Rank 3rd**		**Rank 6th**	**Tisl**	0.89 (0.62, 1.31)	0.79 (0.53, 1.19)	0.79 (0.44, 1.42)	0.76 (0.49, 1.21)
0.76 (0.36, 1.58)	0.90 (0.47, 1.76)	**Tori**	**Rank 4th**		**Rank 5th**	**Nivo**	0.89 (0.61, 1.27)	0.88 (0.51, 1.54)	0.86 (0.56, 1.29)
0.71 (0.34, 1.49)	0.85 (0.43, 1.67)	0.94 (0.43, 2.04)	**Tisl**	**Rank 5th**		**Rank 4th**	**Cemi**	1.00 (0.56, 1.79)	0.97 (0.52, 1.78)
0.69 (0.34, 1.40)	0.83 (0.44, 1.55)	0.91 (0.44, 1.90)	0.97 (0.47, 2.03)	**Sint**	**Rank 6th**		**Rank 3rd**	**Sinti**	0.97 (0.61, 1.52)
0.68 (0.37, 1.26)	0.81 (0.47, 1.39)	0.90 (0.47, 1.73)	0.96 (0.49, 1.87)	0.99 (0.53, 1.83)	**Cemi**	**Rank 7th**		**Rank 2nd**	**Camr**
0.60 (0.30, 1.19)	0.71 (0.39, 1.31)	0.79 (0.38, 1.62)	0.84 (0.41, 1.74)	0.87 (0.43, 1.73)	0.88 (0.48, 1.61)	**Pemb**	**Rank 8th**		**Rank 1st**
0.53 (0.29, 0.99)	0.64 (0.37, 1.08)	0.71 (0.37, 1.36)	0.75 (0.39, 1.45)	0.77 (0.42, 1.43)	0.78 (0.47, 1.31)	0.89 (0.49, 1.63)	**Durv**	**Rank 9th**	
0.52 (0.28, 0.93)	0.63 (0.37, 1.02)	0.69 (0.36, 1.29)	0.74 (0.38, 1.38)	0.76 (0.41, 1.35)	0.77 (0.46, 1.24)	0.88 (0.48, 1.53)	0.98 (0.59, 1.57)	**Nivo**	**Rank 10th**
0.52 (0.26, 1.04)	0.62 (0.34, 1.15)	0.69 (0.34, 1.41)	0.73 (0.36, 1.52)	0.75 (0.38, 1.51)	0.76 (0.42, 1.40)	0.87 (0.45, 1.71)	0.98 (0.54, 1.78)	0.99 (0.57, 1.82)	**Atez**
0.37 (0.23, 0.61)	**0.44 (0.30, 0.65)**	**0.49 (0.28, 0.84)**	**0.52 (0.30, 0.91)**	**0.54 (0.33, 0.88)**	**0.54 (0.38, 0.79)**	0.62 (0.39, 1.00)	0.69 (0.48, 1.00)	0.71 (0.52, 1.00)	0.71 (0.44, 1.14)

Figure 7. Network meta-analysis for OS and PFS of patients with squamous NSCLC. HR with 95% confidence interval are presented for various treatment regimens, including PD-1/PD-L1 inhibitors and chemotherapy. Both direct and indirect comparison results for patients with squamous NSCLC are illustrated, showing the comparative efficacy of each therapy in extending OS and PFS. For comparisons of the OS (right upper half) and PFS (left lower half), a HR <1 favors the column defining treatment. Significant differences are boldly shown in the figure. Chem, chemotherapy; Durv, durvalumab; Atez, atezolizumab; Nivo, nivolumab; Pemb, pembrolizumab; Cemi, cemiplimab; Tisl, tislelizumab; Tori, toripalimab; Sint, sintilimab; Suge, sugemalimab; Camr, camrelizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer.

ES-SCLC in either China or the United States; however, the margin of cost-effectiveness was narrow in China, while it was clearly not cost-effective in the United States. This discrepancy may be attributed to differences in healthcare systems, willingness-to-pay thresholds and drug costs between the two countries (50). Tislelizumab is primarily used in Chinese populations and has been included in the National Medical Insurance Drug List in China. By contrast, as a newly launched drug in other countries, its insurance coverage may not yet be widespread, resulting in high prices that affect patient accessibility. A study examining Black patients with metastatic lung cancer treated with pembrolizumab found that the safety profile and treatment response were similar to those of White patients (51). Pembrolizumab was launched earlier than tislelizumab, and research has shown that the efficacy and safety of tislelizumab combined with chemotherapy are similar to those of pembrolizumab combined with chemotherapy (52). In a real-world study, no significant differences were found in the efficacy and safety of domestically produced tislelizumab and camrelizumab compared with imported pembrolizumab (53). In the present study, nivolumab stood out when used in combination with chemotherapy. This combination approach highlights the potential of nivolumab in improving survival outcomes in patients with advanced NSCLC. In the present study, as a monotherapy, nivolumab also showed notable efficacy, offering flexibility in treatment planning. The choice to use nivolumab, particularly in combination therapy, should be guided by the goal of maximizing survival benefits, especially in advanced disease stages. However, in certain cases, such as patients with significant comorbidities or a preference for maintaining quality of life, treatment decisions may prioritize palliation or minimizing toxicities over aggressive survival-focused strategies. A recent studies has shown that the combination of nivolumab and ipilimumab can serve as a promising new first-line treatment option for patients with advanced NSCLC, as it leads to significant improvements in OS while maintaining a favorable risk-benefit profile (54).

The rapid advancement of domestic PD-1/PD-L1 antibody drugs has introduced new options for cancer immunotherapy in China, increasing the treatment standards for patients across the country. These drugs have not only demonstrated comparable efficacy and safety as imported alternatives but also offer economic advantages, thereby enabling more patients to access effective treatment. A previous randomized clinical trial revealed that patients with resectable stage IIIA or IIIB (T3N2) NSCLC experienced a significant improvement in the pathological complete response rate when treated with camrelizumab plus chemotherapy as opposed to chemotherapy alone and demonstrated good tolerance to adverse effects (55). Grade 3 adverse events that occurred at a rate of ≥1% included anemia, hypernatremia and pulmonary infection (56). Sugemalimab ranked highly for both OS and PFS in the present study. From the perspective of the Chinese health care system, the use of sugemalimab in combination with platinum-based chemotherapy as a first-line treatment for squamous or non-squamous metastatic NSCLC may be more cost-effective than the use of a placebo plus platinum-based chemotherapy (57). This makes sugemalimab a valuable option for improving patient outcomes while also considering its economic feasibility in clinical practice.

Whereas the general safety profile of PD-1/PD-L1 inhibitors appeared favorable in terms of TRAEs, the results of the present study highlighted a concerning aspect with respect to irAEs. At present, the mechanisms underlying the occurrence of irAEs have not been fully elucidated and different organs may have distinct pathological drivers for them (58). As T cells are considered key to the antitumor responses triggered by ICIs and are commonly found to dominate immune cell infiltrates in tissue biopsies of irAEs across various organ systems, a previous study investigated the connection between T cells in irAEs and their corresponding tumors (59). In addition, certain irAEs are associated with autoantibodies similar to those seen in classical autoimmune diseases, and there is evidence regarding the involvement of autoantibodies and B cell responses in both irAEs and antitumor responses (60). Although the reported incidence of severe irAEs has been low thus far, an increase in clinically significant toxicities is inevitable, especially with the increasing use of ICIs (61). The focus on safety can significantly influence treatment choices for NSCLC, guiding clinicians to weigh the benefits of PD-1/PD-L1 therapy against the risk of severe toxicity, ultimately leading to more personalized and safer treatment protocols. ICIs enhance antitumor effects by restoring the function of suppressed effector T cells, making them prone to induce checkpoint inhibitor pneumonitis (CIP) during the treatment of NSCLC (4). Given the risk of irAEs, clinicians are advised to assess the immune status of the patient and the history of autoimmune diseases carefully before initiating ICI therapy. Monitoring for early symptoms of CIP is crucial, as timely intervention can mitigate severe complications. Specifically, in the present study, cemiplimab and pembrolizumab demonstrated greater susceptibility to severe irAEs of grade ≥3 than chemotherapy, indicating a notably increased risk of these events. By contrast, another study has shown that cemiplimab exhibits balanced efficacy and safety in the treatment of advanced NSCLC, which may be attributed to differences in the safety evaluation criteria (62).

In the present study, in non-squamous NSCLC, toripalimab exhibited the most significant benefit. Another NMA recommended pembrolizumab plus chemotherapy, tislelizumab plus chemotherapy and sintilimab plus chemotherapy as effective treatment options for patients with non-squamous NSCLC and PD-L1 expression ≥50% (63). It was evident that PD-L1 expression was a crucial factor to consider when selecting PD-1/PD-L1 inhibitors. In the present study, compared with chemotherapy, cemiplimab, camrelizumab, tislelizumab and nivolumab were associated with a longer OS time in patients with squamous NSCLC. These histology-specific findings highlight the importance of tailored treatment approaches on the basis of tumor characteristics.

Despite the strengths of the NMA performed in the present study, including its comprehensive nature and large sample size, certain limitations must be acknowledged. Potential heterogeneity across the included studies, variations in follow-up periods and possible publication bias may have influenced the interpretation of the results. Moreover, the lack of direct head-to-head comparisons between all the inhibitors necessitated a cautious interpretation of the indirect comparison results.

In conclusion, the choice of PD-1/PD-L1 inhibitor should be tailored to individual patient needs, balancing efficacy with safety profiles. Tislelizumab, pembrolizumab and nivolumab are highly effective options for improving survival outcomes. By contrast, camrelizumab and cemiplimab offer notable benefits in terms of PFS but require careful management of side effects. Long-term follow-up studies are needed to confirm the durability of the observed survival benefits.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZZ and KY contributed to the conception and design of the study. Data collection was performed by LL and YW, statistical analysis was performed by LL and YY and interpretation of the data was performed by LY and ZL. LL and YY drafted and revised the manuscript. ZZ and KY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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