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Research article

Dual immunotherapy in advanced or metastatic non-small cell lung cancer: A network meta-analysis

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ABATRACT

Objectives: Recently, there has been extensive research on dual immunotherapy for advanced or metastatic non-small cell lung cancer (NSCLC), yet a comprehensive evaluation is lacking. This study aimed to rank the available treatment options and assess the efficacy and safety of dual immunotherapy regimens through the implementation of a Bayesian network meta-analysis (NMA).

Materials and methods: A thorough search was conducted to recognize eligible randomized controlled trials (RCTs) on March 20, 2023. Overall survival (OS), progression-free survival (PFS), treatment-related adverse events (TRAEs) and grade ≥3 TRAEs were evaluated to identify the efficacy and safety of dual immunotherapy regimens. The surface under the cumulative ranking curve (SUCRA) and *P* score were employed to rank the treatments.

Results: Eleven clinical trials involving six different regimens were included in this study. The combination of anti-programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) antibodies with anti-T-cell immunoglobulin and ITIM domain (TIGIT) antibodies emerged as the most promising regimen for improving OS and PFS, followed by anti-PD-1/PD-L1 + anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) + chemotherapy treatment and anti-PD-1/PD-L1 + anti-CTLA-4 treatment. The forest plots demonstrated that these three regimens were all superior to chemotherapy. The above results were observed in both unselected treatment line and first-line settings. The least likely to be associated with TRAEs and grade ≥3 TRAEs were respectively anti-CTLA-4 treatment and anti-PD-1/PD-L1 + anti-TIGIT treatment, with anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment to be the worst.

Conclusions: This NMA validated the promising efficacy and safety of dual immunotherapy in advanced or metastatic NSCLC. Among them, anti-PD-1/PD-L1 + anti-TIGIT regimen emerges as a highly potential therapeutic approach. Ongoing research efforts should focus on improving treatment regimens, identifying biomarkers, and managing TRAEs to optimize the patient benefits of dual immunotherapy.

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1. Introduction

Lung cancer, a leading cause of cancer-related deaths globally, remains one of the most prevalent malignant tumors [1,2]. It encompasses two main types: NSCLC, constituting approximately 80–85% of all cases, and SCLC, making up roughly the residual 15% of occurrences [3–5]. The prognosis for metastatic lung cancer remains poor, with a mere 4% 5-year survival rate [6].

Despite significant advancements over the past few decades, conventional treatment options including chemotherapy, targeted therapy and radiation therapy continue to face constraints in improving patient survival [7]. However, the advent of immunotherapy has brought a fresh outlook for lung cancer patients. The application of immune checkpoint inhibitors (ICIs) has significantly increased the 5-year survival rate of advanced NSCLC from 5% to 30% [8]. Currently approved or under investigation ICIs include PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, TIGIT inhibitors, lymphocyte-activation gene 3 (LAG-3) inhibitors, T-cell immunoglobulin domain and mucin domain-3 (TIM-3) inhibitors, V-domain immunoglobulin suppressor of T cell activation (VISTA) inhibitors, and others. However, the monotherapy efficacy of ICIs in advanced NSCLC is only around 20%–30% [9].

To explore more efficient and less toxic immunotherapy strategies, numerous researches focus on combining ICIs with chemotherapy, radiotherapy, targeted therapy, anti-tumor angiogenesis therapy, as well as dual immunotherapy and multi-mechanism combination therapy [10]. Bibliometric analysis is a method that aids in understanding research trends [11], revealing that dual immunotherapy has emerged as a research hotspot [12]. Currently, dual immunotherapy approaches mainly involve the combination of PD-1/PD-L1 inhibitors with CTLA-4 inhibitors, PD-1/PD-L1 inhibitors with TIGIT inhibitors, PD-1/PD-L1 inhibitors with LAG-3 inhibitors, and others. These approaches have demonstrated broad application prospects in extensive large-scale clinical trials, gradually shifting from the back-line to the first-line and even the perioperative period.

Multiple researches have assessed the feasibility of dual immunotherapy for managing NSCLC patients. The CheckMate 227 study [13] and CheckMate 9LA study [14] respectively validated the efficacy of nivolumab + ipilimumab alone or together with two cycles of chemotherapy for advanced NSCLC treatment. Regarding the durvalumab plus tremelimumab regimen, ARCTIC study [15], MYSTIC study [16], and NEPTUNE study [17] showed its inferior efficacy compared to standard chemotherapy, while POSEIDON study revealed that combining durvalumab plus tremelimumab with chemotherapy resulted in greater effectiveness than chemotherapy [18]. Additionally, the KEYNOTE 598 study revealed that the feasibility of pembrolizumab combined with ipilimumab were not as promising [19]. Moreover, the CITYSCAPE study [20] and TACTI-002 study [21,22] respectively provided preliminary evidence for the effectiveness of PD-1/PD-L1 inhibitors plus TIGIT inhibitors and PD-1/PD-L1 inhibitors plus LAG-3 inhibitors in NSCLC treatment. Considering the contradictory results of dual immunotherapy approaches in NSCLC, we conducted a NMA to determine whether dual immunotherapy regimens were able to improve the patient outcomes.

NMA allows for the aggregation and synthesis of results from multiple clinical trials, thereby, providing more reliable evidence and a comprehensive understanding of dual immunotherapy for NSCLC. This study innovatively incorporated the emerging dual immunotherapy approach of PD-1/PD-L1 inhibitors plus TIGIT inhibitors. We focused on evaluating the effectiveness and safety of this method compared to other dual immunotherapy approaches. Through our comprehensive analysis, we hope to explore the potential and advantages of this treatment strategy in NSCLC management, thereby providing recommendations for future research direction and clinical practice.

2. Materials and methods

2.1. Data sources and search strategy

Our NMA was conducted on March 20, 2023, utilizing PubMed, EMBASE, and Cochrane databases. The search terms comprised NSCLC and immunotherapy agents, including anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-LAG-3, anti-TIGIT, anti-TIM-3, and anti-VISTA, as listed in Supplementary Table 1. Additionally, we searched for updated outcomes by reviewing abstracts and presentations from leading international conferences, such as the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), American Association for Cancer Research (AACR), World Conference on Lung Cancer (WCLC), and Chinese Society of Clinical Oncology (CSCO).

2.2. Study selection

To ensure accuracy, all search results were independently evaluated by two researchers. In instances of discrepancies, resolution was achieved through deliberation or with the assistance of a third researcher. The studies deemed eligible had to fulfill the subsequent criteria: (1) prospective RCTs involving patients with histologically or cytologically confirmed NSCLC, (2) the intervention group received two ICIs concurrently, (3) outcomes included OS or PFS, and (4) the language is English.

We excluded observational studies, non-randomized trials, case reports, letters, editorials, reviews, and studies with insufficient data. Similarly, single-arm or dosage-finding trials were not considered. In cases where multiple publications presented findings from identical clinical trials, we exclusively integrated the latest available data. Fig. 1 illustrated the literature screening process.

2.3. Data Extraction and quality assessment

All included clinical trials were analyzed to extract the following information: study name, first author, National Clinical Trials identification number, trial phase, clinicopathological characteristics, sample size, intervention regimen, control treatment, safety and

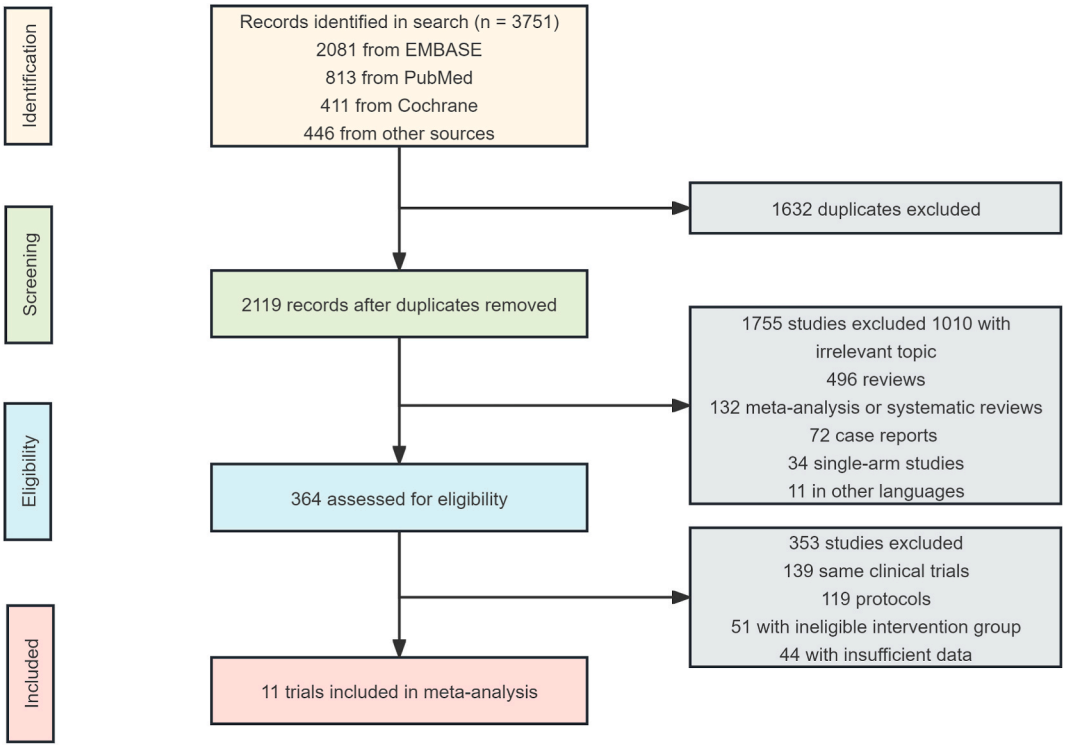

Fig. 1. Flow chart of literature screening.

survival data. To assess the efficacy of dual immunotherapy regimens in NSCLC, hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS were obtained from the most recent trial analysis with the longest follow-up. Additionally, the number of patients with TRAEs for all grades and for grade 3 or higher was also extracted for safety analysis.

This NMA adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. The Cochrane risk of bias assessment tool was utilized to check the quality of the included studies. Two independent investigators assessed the risk of bias in seven domains, encompassing random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. In the event of any discrepancies, resolutions were reached through discussions with co-authors. The quality of enrolled RCTs was judged using RevMan statistical software (version 5.3) and presented in Supplementary Fig. 1.

2.4. Statistical analysis

We conducted the NMA in the Bayesian framework to assess direct and indirect evidence, using "JAGS" and "Gemtc" packages in R 4.1.0 [23]. The endpoints of this NMA were OS and PFS, which were described as HRs with corresponding 95% CIs for each trial and safety outcomes were expressed as odds ratios (ORs). We pooled HRs and ORs using the fixed or random model and determined the consistency of our model by deviance information criteria (DIC). To rank treatments, we employed the *P* score, a frequentist counterpart to the SUCRA. The "ggplot 2" package in R was used to perform the SUCRA to present rank probability. Statistical heterogeneity was evaluated using the I^2 statistic, with an I^2 value exceeding 50% typically indicating significant heterogeneity, prompting the need for sensitivity analysis to identify its source. Various diagnostic plots, including trace plots, density plots, and Brooks-Gelman-Rubin diagnostic plots were utilized to ensure the convergence of model. We considered convergence satisfactory when we observed a smooth density curve close to a normal distribution, trace plots without significant fluctuations, and Brooks-Gelman-Rubin diagnostic plots with 97.5% values of the reduction factor and potential scale reduction factor (PSRF) approaching 1 and stabilizing, respectively. All tests were two-sided, and a *P*-value below 0.05 was regarded as statistically significant.

3. Results

3.1. Study characteristics of NMA

Eleven RCTs were eligible for our NMA, comprising 4987 patients with any PD-L1 level across 16 different treatments. These treatments included anti-PD-1/PD-L1 + anti-TIGIT regimens (e.g., atezolizumab + tiragolumab [20], zimberelimab + domvanalimab

Table 1
Baseline characteristics of studies included in the network meta-analysis.

Number	Study	First Author	Register Number	Phase	Mutations	PD-L1 Expression	Cancer Type	ECOG	Treatment Line	Study Arms	Sample Size	Median PFS (mo) (95% CI)	PFS Hazard Ratio (95% CI)	Median OS (mo) (95% CI)	OS Hazard Ratio (95% CI)	TRAE rate	Grade ≥3 TRAE rate	Median Follow-up Time (mo) (95% CI)
1	CITYSCAPE	Byoung Chul Cho	NCT03563716	II	no EGFR or ALK alterations	TPS ≥1%	Locally advanced unresectable or metastatic NSCLC	PS ≤ 1	First-line	Atezolizumab + Tiragolumab	67	5.6 (4.2–10.4)	0.62 (0.42–0.91)	23.2 (14.1–31.5)	0.69 (0.44–1.07)	82%	21%	5.9 (4.6–7.6)
										Atezolizumab	68	3.9 (2.7–4.5)		14.5 (9.6–20.4)		71%	18%	
2	ARC-7	Melissa Lynne Johnson	NCT04262856	II	no EGFR or ALK alterations	TPS ≥50%	Metastatic NSCLC	PS ≤ 1	First-line	Zimberelimab + Domvanalimab	44	12.0 (5.5 - NE)	0.55 (0.31–1.0)	–	–	47%	47%	11.8
										Zimberelimab	44	5.4 (1.8–9.6)		–		48%	58%	
3	–	Cheng, Y	NCT04672369	I	driver gene negative	TPS ≥50%	Advanced NSCLC	PS ≤ 1	First-line	Sintilimab + IBI939	28	NR (6.8 - NE)	0.43 (0.17–1.10)	–	–	85.7%	7.1%	–
										Sintilimab	14	6.0 (1.4 - NE)		–		71.4%	35.7%	
4	CheckMate 227	Julie R. Brahmer	NCT02477826	III	No EGFR or ALK alterations	–	Stage IV or recurrent NSCLC	PS ≤ 1	First-line	Nivolumab + Ipilimumab	583	5.1 (4.2–5.7)	0.78 (0.68–0.89)	17.2 (15.3–20.0)	0.73 (0.64–0.83)	77%	33%	66.7
										Chemotherapy	583	5.5 (4.6–5.6)		13.9 (12.2–15.1)		82%	36%	
5	Lung-MAP S1400I	Scott N. Gettinger	NCT02785952	III	–	–	Stage IV squamous cell lung cancer	PS ≤ 1	Second-line	Nivolumab + Ipilimumab	125	3.8 (2.7–4.4)	0.80 (0.61–1.03)	10 (8.0–14.4)	0.87 (0.66–1.16)	66%	39.5%	29.5 (26.0–32.8)
										Nivolumab	127	2.9 (1.8–4.0)		11 (8.6–13.7)		59%	33.3%	
6	CheckMate 9LA	M. Reck	NCT03215706	III	no EGFR or ALK alterations	–	Stage IV or recurrent NSCLC	PS ≤ 1	First-line	Nivolumab + Ipilimumab + Chemotherapy	361	6.7 (5.6–7.8)	0.67 (0.56–0.79)	15.8 (13.9–19.7)	0.72 (0.61–0.86)	92%	48%	30.7
										Chemotherapy	358	5.3 (4.4–5.6)		11.0 (9.5–12.7)		88%	38%	
7	KEYNOTE-598	Michael Boyer	NCT03302234	III	no EGFR or ALK alterations	TPS ≥50%	Stage IV metastatic NSCLC	PS ≤ 1	First-line	Pembrolizumab + Ipilimumab	284	8.2 (6.0–10.5)	1.06 (0.86–1.30)	21.4 (16.6 - NE)	1.08 (0.85–1.37)	96.5%	62.4%	20.6 (12.4–31.7)
										Pembrolizumab	284	8.4 (6.3–10.5)		21.9 (18.0 - NE)		93.6%	50.2%	
8	NEPTUNE	Gilberto de Castro	NCT02542293	III	no EGFR or ALK alterations	–	Advanced or metastatic NSCLC with bTMB ≥20 mut/Mb	PS ≤ 1	First-line	Durvalumab + Tremelimumab	69	4.2 (2.7–5.6)	0.77 (0.51–1.15)	11.7 (8.6–15.2)	0.71 (0.49–1.05)	68.3%	20.7%	35.0 (4. 2–42.5)
										Chemotherapy	60	5.1 (4.2–5.6)		9.1 (7.8–12.6)		81.5%	33.6%	
9	MYSTIC	Naiyer A. Rizvi	NCT02453282	III	no EGFR or ALK alterations	TPS ≥25%	Stage IV metastatic NSCLC	PS ≤ 1	First-line	Durvalumab + Tremelimumab	372	3.9 (2.8–5.0)	1.05 (0.72–1.53)	11.9 (9.0–17.7)	0.85 (0.61–1.17)	60.1%	22.9%	10.6 (0–18) for PFS
										Chemotherapy	372	5.4 (4.6–5.8)		12.9 (10.5–15.0)		83%	33.8%	30.2 (0.3–37.2) for OS

(*continued on next page*)

Table 1 (*continued*)

Number	Study	First Author	Register Number	Phase	Mutations	PD-L1 Expression	Cancer Type	ECOG	Treatment Line	Study Arms	Sample Size	Median PFS (mo) (95% CI)	PFS Hazard Ratio (95% CI)	Median OS (mo) (95% CI)	OS Hazard Ratio (95% CI)	TRAE rate	Grade ≥3 TRAE rate	Median Follow-up Time (mo) (95% CI)
10	ARCTIC	D. Planchard	NCT02352948	III	no EGFR or ALK alterations	TPS <25%	Locally advanced or metastatic NSCLC (Stage IIIB-IV)	PS ≤ 1	Third-line or later treatment	Durvalumab + Tremelimumab	174	3.5 (2.3–4.6)	–	11.5 (8.7–14.1)	–	92.5%	42.8%	9.1 (0–32.8)
										SOC	118	3.5 (1.9–3.9)	0.77 (0.59–1.01)	8.7 (6.5–11.7)	0.80 (0.61–1.05)	95.5%	51.8%	
										Durvalumab	117	3.1 (1.9–3.7)	0.87 (0.68–1.12)	10.0 (7.1–13.2)	0.98 (0.74–1.30)	93.2%	36.8%	
										Tremelimumab	60	2.1 (1.8–3.2)	0.67 (0.49–0.92)	6.9 (3.9–13.2)	0.78 (0.56–1.11)	85%	41.7%	
11	POSEIDON	Melissa L. Johnson	NCT03164616	III	no EGFR or ALK alterations	–	Stage IV metastatic NSCLC	PS ≤ 1	First-line	Durvalumab + Tremelimumab + Chemotherapy	338	6.2 (5.0–6.5)	0.72 (0.60–0.86)	14.0 (11.7–16.1)	0.77 (0.65–0.92)	92.7%	51.8%	10.3 (0.0–23.1) for PFS 34.9 (0.0–44.5) for OS
										Chemotherapy	337	4.8 (4.6–5.8)		11.7 (10.5–13.1)		89.5%	44.4%	

TPS, tumor proportion score; bTMB, blood tumor mutational burden; mut/Mb, mutations per megabase; mo, month; NR, not reach; NE, not evaluable.

[24], sintilimab + IBI939 [25]), anti-PD-1/PD-L1 + anti-CTLA-4 regimens (e.g., nivolumab + ipilimumab [26,27], pembrolizumab + ipilimumab [28], durvalumab + tremelimumab [15–17]), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy regimens (e.g., nivolumab + ipilimumab + chemotherapy [29], durvalumab + tremelimumab + chemotherapy [18]), anti-PD-1/PD-L1 regimens (e.g., atezolizumab [20], durvalumab [15], zimberelimab [24], sintilimab [25], nivolumab [27], pembrolizumab [28]), anti-CTLA-4 regimens (e.g., tremelimumab [15]), and chemotherapy [15–18,26,29]. This research compared the effectiveness and safety of distinct dual immunotherapy regimens for NSCLC. Except for the Lung-MAP S1400I and ARTIC clinical trials, all other clinical trials included patients in the first-line treatment. The Lung-MAP S1400I study and the ARTIC study were respectively designed as second-line treatment and third-line or later treatment in patients with chemotherapy-pretreated, immunotherapy-naive advanced NSCLC. The CheckMate 9LA study and the POSEIDON study investigated the efficacy of dual immunotherapy combined with chemotherapy compared to chemotherapy alone, while other clinical trials focused on exploring the effectiveness of dual immunotherapy compared to chemotherapy or single ICI. Notably, clinical trials involving anti-PD-1/PD-L1 + anti-CTLA-4 regimens were all phase III, whereas clinical trials involving anti-PD-1/PD-L1 + anti-TIGIT regimens were phase I or II. Patients in all trials had an Eastern Cooperative Oncology Group (ECOG) performance status score less than 1. Only one study included squamous cell carcinoma and did not select for genetic mutations, while the others involved NSCLC without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations. All clinical trials comprised a minimum of two treatment groups, and the study characteristics were shown in Table 1.

3.2. NMA of OS

Nine studies of six kinds of treatments were included for OS (Fig. 2A). Pooled mixed comparison results were presented as forest plots in Fig. 3. Compared with chemotherapy, anti-PD-1/PD-L1 + anti-TIGIT treatment (HR: 0.53, 95% CI: 0.32–0.91) (Fig. 3A), anti-PD-1/PD-L1 + anti-CTLA-4 treatment (HR: 0.76, 95% CI: 0.66–0.89) (Fig. 3B), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (HR: 0.75, 95% CI: 0.62–0.89) (Fig. 3C) and anti-PD-1/PD-L1 treatment (HR: 0.77, 95% CI: 0.62–0.98) (Fig. 3D) all had better OS (Fig. 3F). Anti-CTLA-4 therapy was the only ICI regimen that did not have significant benefit over chemotherapy (HR: 0.98,

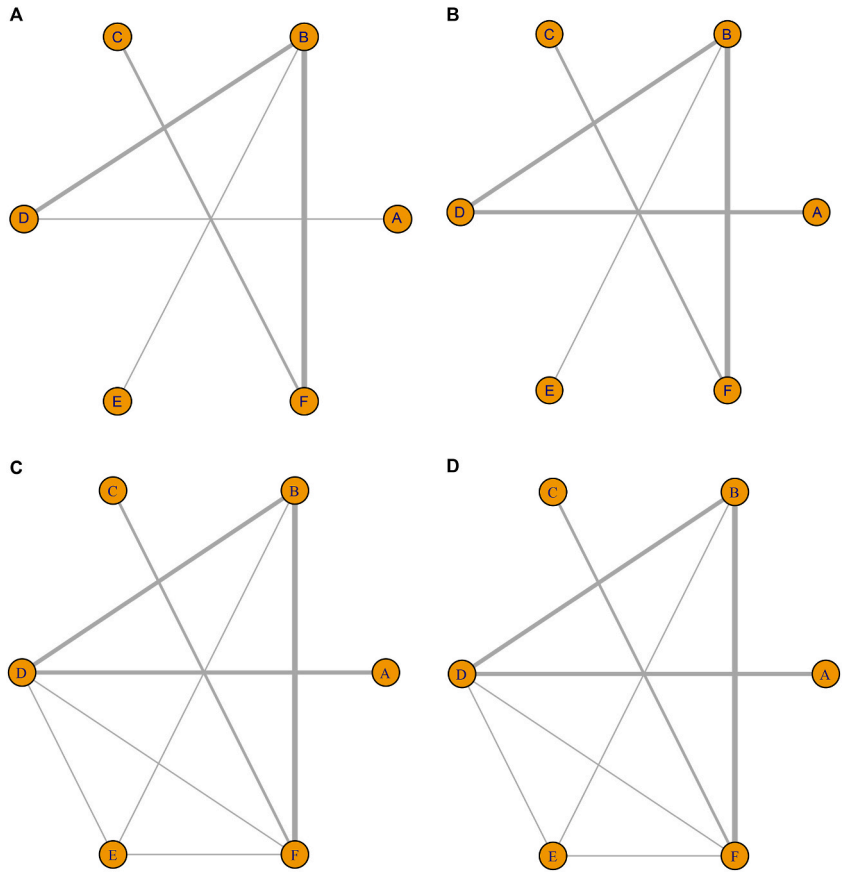

Fig. 2. Network plots of comparisons for OS **(A)**, PFS **(B)**, TRAEs **(C)**, grade ≥3 TRAEs **(D)** of different regimens in unselected treatment line setting. Each node represents a treatment regimen. The thickness of the line represents the number of related clinical trials. Treatment A: anti-PD-1/PD-L1 + anti-TIGIT treatment. Treatment B: anti-PD-1/PD-L1 + anti-CTLA-4 treatment. Treatment C: anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment. Treatment D: anti-PD-1/PD-L1 treatment. Treatment E: anti-CTLA-4 treatment. Treatment F: chemotherapy.

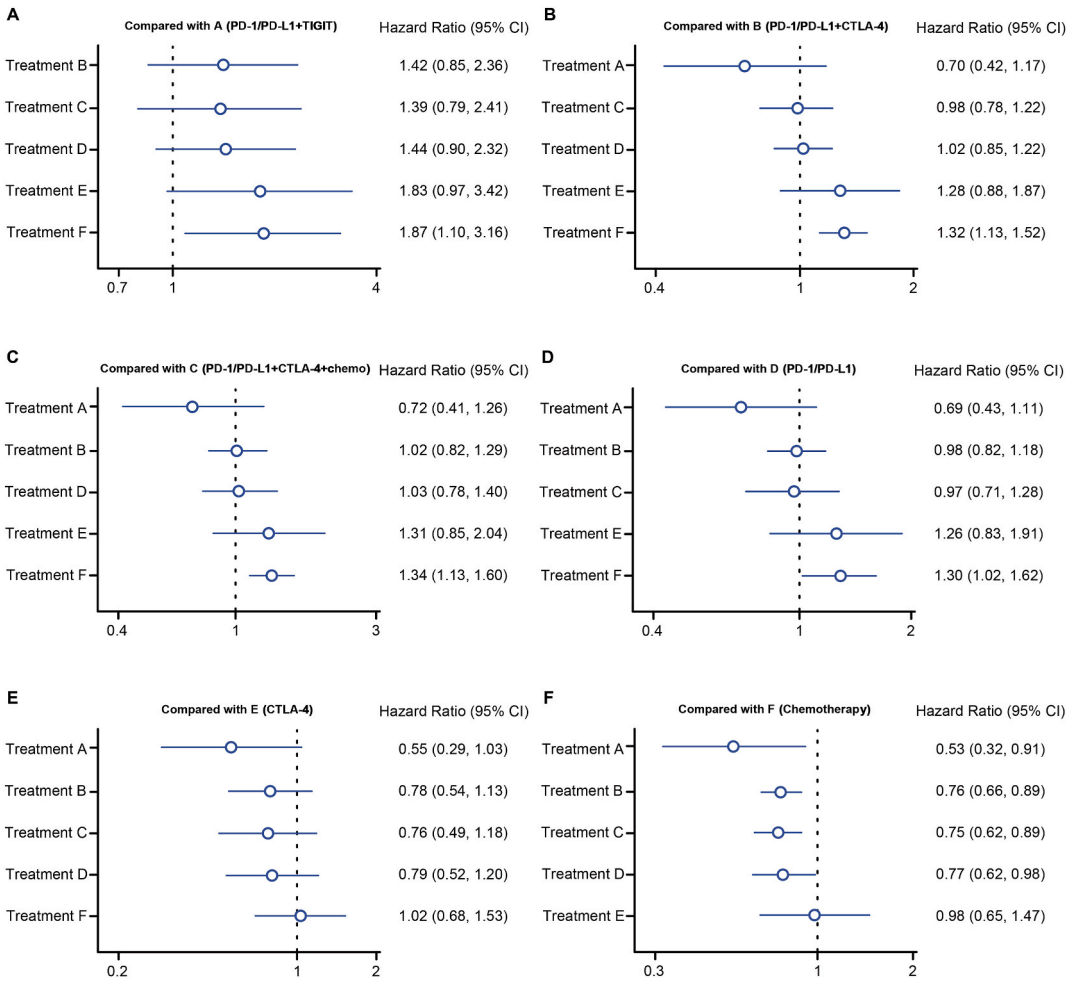

Fig. 3. Forest plots of the relative effects of OS in unselected treatment line setting. The meaning of Treatment A-F is as described above.

95%CI, 0.65–1.47) (Fig. 3E–F). No other significant differences were observed between treatments, suggesting that both single and dual immunotherapies based on anti-PD-1/PD-L1 therapy have demonstrated superior efficacy in comparison to chemotherapy. According to SUCRA score of OS, anti-PD-1/PD-L1 + anti-TIGIT treatment ranked first (probability: 0.93), followed by anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (probability: 0.64), anti-PD-1/PD-L1 + anti-CTLA-4 treatment (probability: 0.60), anti-PD-1/PD-L1 treatment (probability: 0.54), anti-CTLA-4 treatment (probability: 0.19) and chemotherapy (probability: 0.10). Therefore, anti-PD-1/PD-L1 + anti-TIGIT treatment was likely to be the best option among all dual immunotherapy regimens for improving OS (Fig. 4A).

The results of the convergence assessment of the model were shown in the Supplementary Figs. 2–4. From the trace plots, density plots, and Brooks-Gelman-Rubin diagnostic plots, the model exhibited good convergence. The DIC analysis suggested that the consistency model and the inconsistency model had similar fit to the data (14.42 vs. 14.54). As presented in Supplementary Fig. 5, the assessment of overall heterogeneity revealed that the heterogeneity was low for OS ($I^2 = 0\%$).

3.3. NMA of PFS

All eleven clinical trials reported data on PFS and were included in our analysis (Fig. 2B). As shown in Fig. 5, the population treated with anti-PD-1/PD-L1 + anti-TIGIT treatment (Fig. 5A) were more likely to obtain better PFS than those received anti-PD-1/PD-L1 + anti-CTLA-4 treatment (HR: 0.62, 95% CI: 0.42–0.92) (Fig. 5B), anti-PD-1/PD-L1 treatment (HR: 0.57, 95% CI: 0.41–0.80) (Fig. 5D), anti-CTLA-4 treatment (HR: 0.42, 95% CI: 0.25–0.72) (Fig. 5E) or chemotherapy (HR: 0.50, 95% CI: 0.33–0.77) (Fig. 5F). The efficacy of anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (HR: 0.73, 95% CI: 0.46–1.16) showed no significant difference from that of anti-PD-1/PD-L1 + anti-TIGIT treatment (Fig. 5C). Both anti-PD-1/PD-L1 + anti-CTLA-4 treatment and anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment demonstrated superior efficacy compared to anti-CTLA-4 treatment (HR: 0.68, 95% CI: 0.46–0.98; HR: 0.58, 95% CI: 0.37–0.90, respectively) (Fig. 5E) or chemotherapy (HR: 0.81, 95% CI: 0.69–0.96; HR: 0.69, 95% CI: 0.57–0.84, respectively) (Fig. 5F). Furthermore, the SUCRA values of PFS analysis revealed that anti-PD-1/PD-L1 + anti-TIGIT treatment

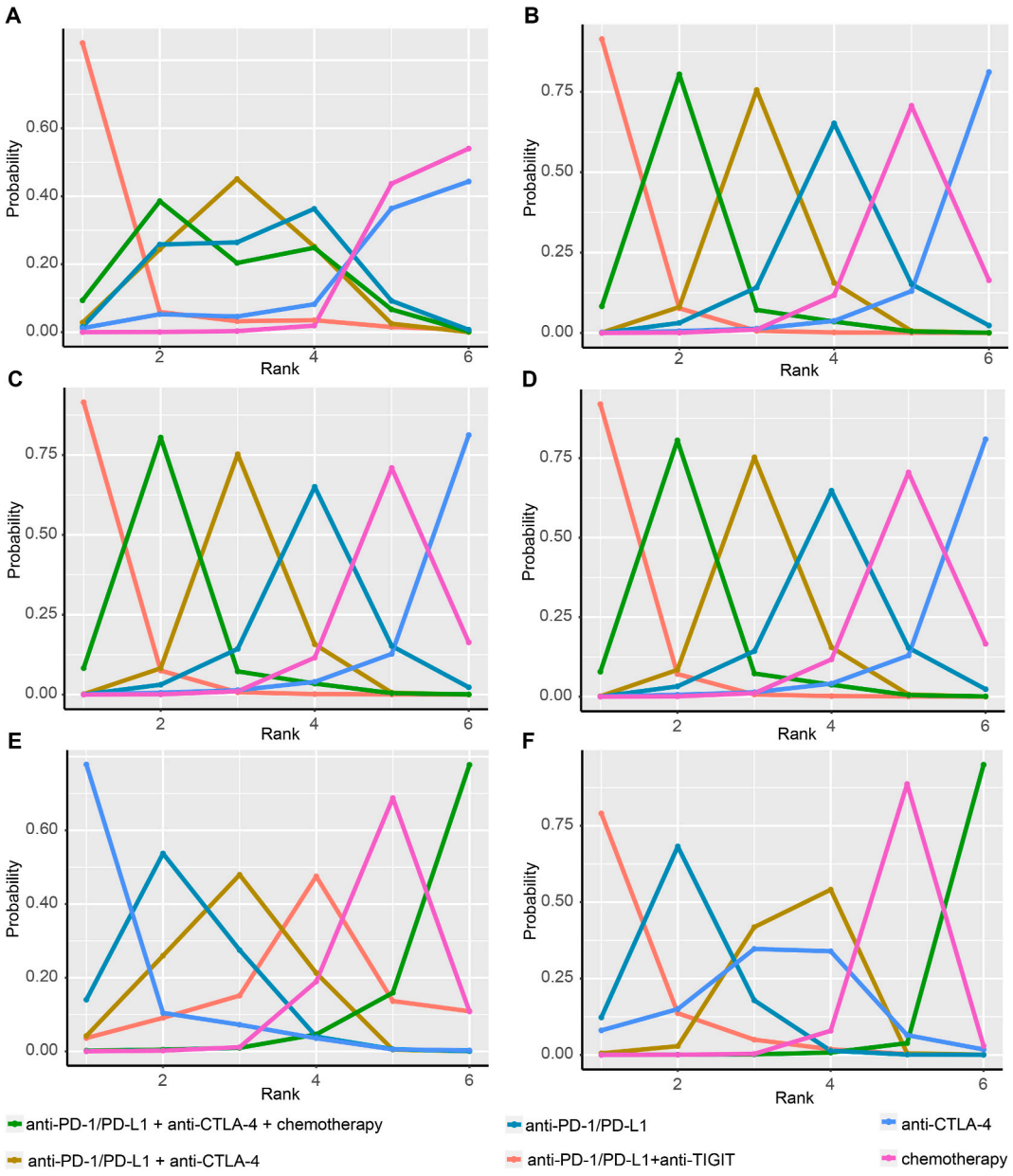

Fig. 4. A, B, C, D: Efficacy profiles illustrate the probability of each comparable treatment being ranked from first to last on OS **(A, C)** and PFS **(B, D)** in unselected treatment line **(A, B)** and first-line **(C, D)** settings. **E, F:** Safety profiles illustrate the probability of each comparable treatment being ranked from first to last on TRAEs for all grades **(E)** and grade ≥3 TRAEs **(F)**. The x-axis represents the probability of the preferential treatment being ranked in nth position.

(probability: 0.98) ranked the best, followed by anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (probability: 0.78), anti-PD-1/PD-L1 + anti-CTLA-4 treatment (probability: 0.58), anti-PD-1/PD-L1 treatment (probability: 0.40), chemotherapy (probability: 0.20), and anti-CTLA-4 treatment (probability: 0.06) ranked sixth (Fig. 4B). Therefore, anti-PD-1/PD-L1 + anti-TIGIT treatment was likely to be the best regimen for prolonging PFS of NSCLC.

The Supplementary Figs. 6–8 presentd the outcomes of evaluating the model's convergence. The trace plots, density plots, and Brooks-Gelman-Rubin diagnostic plots collectively demonstrated satisfactory convergence of the model. DIC values analysis indicated that the consistency model exhibited comparable data fit to the inconsistency model (17.70 vs. 17.70). The Supplementary Fig. 9 provided an overview of the heterogeneity assessment, revealing minimal heterogeneity for OS ($I^2 < 50\%$).

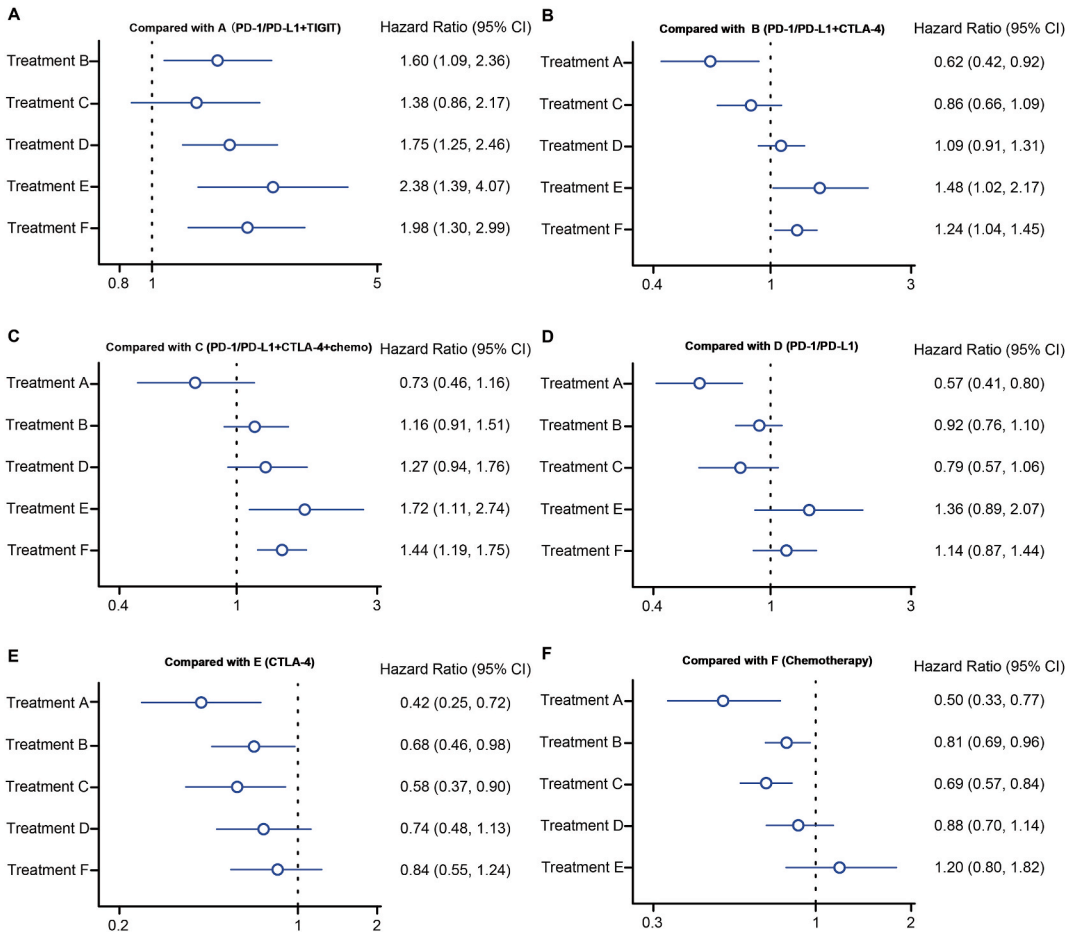

Fig. 5. Forest plots of the relative effects of PFS in unselected treatment line setting. The meaning of Treatment A-F is as described above.

3.4. NMA for the first-line treatment of NSCLC

Considering the superior performance of anti-PD-1/PD-L1 + anti-TIGIT teratment in NSCLC management, its efficacy in first-line therapy was further investigated. A total of 7 clinical trials were included for OS analysis and 9 clinical trials were included for PFS analysis. The ranking profiles of dual immunotherapy regimens in first-line therapy for OS and PFS were shown in Fig. 4C and D, respectively. OS and PFS analysis revealed that, anti-PD-1/PD-L1 + anti-TIGIT treatment ranked first (probability: 0.98, 0.98, respectively), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment ranked second (probability: 0.79, 0.78, respectively), and anti-PD-1/PD-L1 + anti-CTLA-4 treatment ranked third (probability: 0.58, 0.58, respectively). Additionally, the forest plots illustrated that anti-PD-1/PD-L1 + anti-TIGIT treatment (Fig. 6A and 7A), anti-PD-1/PD-L1 + anti-CTLA-4 treatment (Fig. 6B and 7B), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (Fig. 6C and 7C), and anti-PD-1/PD-L1 treatment (Fig. 6D and 7D) all outperformed chemotherapy in both OS (Fig. 6F) and PFS (Fig. 7F). The anti-CTLA-4 therapy did not demonstrate significant differences compared to other treatments in terms of OS (Fig. 6E) and PFS (Fig. 7E).

The trace plots, density plots, and Brooks-Gelman-Rubin diagnostic plots were shown in Supplementary Figs. 10–12 and Supplementary Figs. 14–16, respectively, revealing favorable convergence of the model. By comparing the DIC values, it can be inferred that the consistency model demonstrates a comparable data fit to the inconsistency model (14.63 vs. 14.44, 14.57 vs. 14.67, respectively). The comprehensive evaluation of heterogeneity, as presented in Supplementary Fig. 13 and Supplementary Fig. 17, respectively, indicated minimal heterogeneity for OS and PFS ($I^2 = 0\%$).

3.5. NMA of TRAEs

In the NMA of TRAEs (Fig. 2C) and grade ≥3 TRAEs (Fig. 2D), high heterogeneity was found (Supplememntary Fig. 18 and Supplememntary Fig. 19), and the random-effect model was employed. Safety ranking profiles of TRAEs and grade ≥3 TRAEs were shown in Fig. 4E and F, respectively. The probabilities of becoming the safest choice for TRAEs were as follows: anti-CTLA-4 treatment (probability: 0.92), anti-PD-1/PD-L1 treatment (probability: 0.75), anti-PD-1/PD-L1 + anti-CTLA-4 treatment (probability: 0.62), anti-

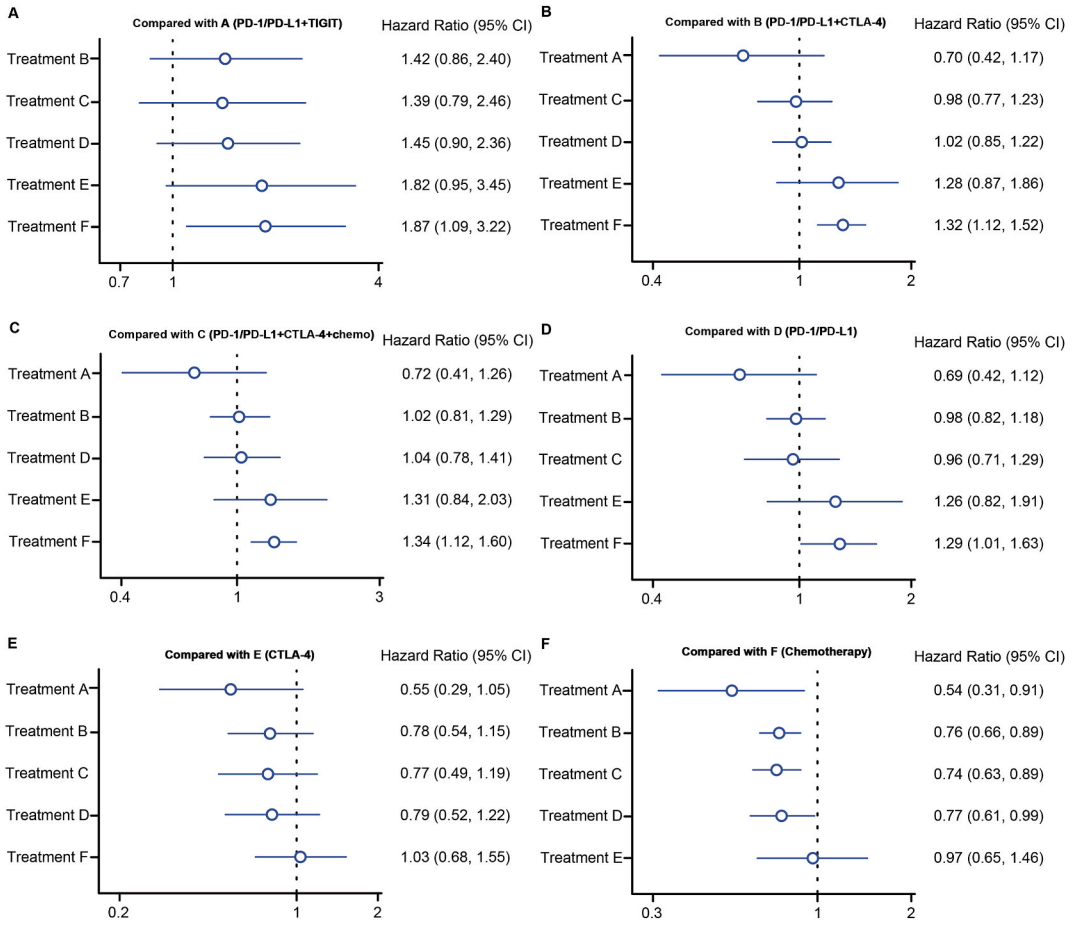

Fig. 6. Forest plots of the relative effects of OS in first-line setting. The meaning of Treatment A-F is as described above.

PD-1/PD-L1 + anti-TIGIT treatment (probability: 0.42), chemotherapy (probability: 0.22), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (probability: 0.06). The treatments least likely to be associated with grade ≥3 TRAEs, in descending order of probability, were anti-PD-1/PD-L1 + anti-TIGIT treatment (probability: 0.94), anti-PD-1/PD-L1 treatment (probability: 0.78), anti-CTLA-4 treatment (probability: 0.56), anti-PD-1/PD-L1 + anti-CTLA-4 treatment (probability: 0.50), chemotherapy (probability: 0.21), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (probability: 0.01). The incidence of TRAEs with anti-PD-1/PD-L1 + anti-TIGIT treatment showed no significant difference compared to other treatment regimens (Fig. 8A). However, it significantly decreased the risk of grade ≥3 TRAEs (Fig. 9A) when compared to anti-PD-1/PD-L1 + anti-CTLA-4 treatment (HR: 0.48, 95% CI: 0.23–0.99) (Fig. 9B), anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (HR: 0.23, 95% CI: 0.09–0.52) (Fig. 9C), or chemotherapy (HR: 0.32, 95% CI: 0.15–0.68) (Fig. 9F). Compared to anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment (Fig. 8C and 9C) or chemotherapy (Fig. 8F and 9F), the incidence rates of TRAEs and grade ≥3 TRAEs with anti-PD-1/PD-L1 + anti-CTLA-4 treatment (Fig. 8B and 9B), anti-PD-1/PD-L1 treatment (Fig. 8D and 9D), and anti-CTLA-4 treatment (Fig. 8E and 9E) all decreased. We observed that treatment regimens involving chemotherapy exhibited higher rates of TRAEs and grade ≥3 TRAEs.

As presented in Supplementary Figs. 20–22 and Supplementary Figs. 23–25, the trace plots, density plots, and Brooks-Gelman-Rubin diagnostic plots revealed favorable convergence of our model. By comparing the DIC values, it can be inferred that the consistency model demonstrates a comparable data fit to the inconsistency model (43.35 vs. 43.32, 45.67 vs. 45.63, respectively).

4. Discussion

NSCLC is characterized by its intricate nature, emphasizing the necessity for a meticulous assessment of existing evidence. Given the evolving landscape of dual immunotherapy, a comprehensive evaluation becomes imperative. By critically examining and synthesizing the data from multiple studies, this NMA aimed to offer a holistic perspective of the present status of dual immunotherapy for NSCLC, shedding light on the potential benefits, limitations, and areas for future exploration in this rapidly evolving field.

This study affirmed the heightened effectiveness of the anti-PD-1/PD-L1 + anti-TIGIT treatment in managing NSCLC. Blocking PD-1 and TIGIT through distinct mechanisms can more effectively restore the co-stimulatory receptor CD226, thereby enhancing the immune activity of $CD8^+$ T cells [30]. Currently, anti-TIGIT antibodies under investigation include domvanalimab, tiragolumab,

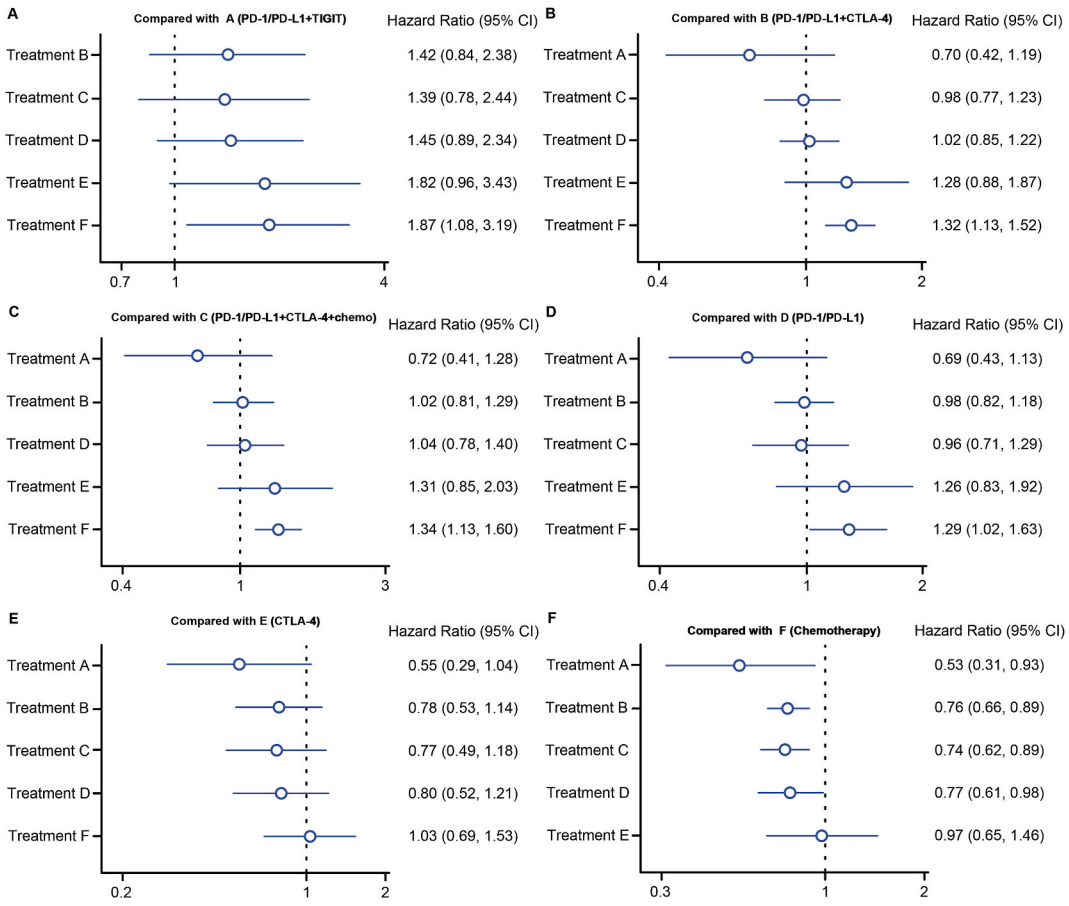

Fig. 7. Forest plots of the relative effects of PFS in first-line setting. The meaning of Treatment A-F is as described above.

vibostolimab, etigilimab, M6223, EOS884448, BMS986207, AB154, ociperlimab, OMP-313M32, IBI-939, and so on [31]. The CITYSCAPE study demonstrated clinical improvements in objective response rate (ORR) and PFS with tiragolumab + atezolizumab compared to atezolizumab as first-line treatment for recurrent or metastatic NSCLC patients with high PD-L1 expression [20]. The SKYSCRAPER-01 study further validated the findings of the CITYSCAPE study. The interim findings indicated that, at a median follow-up time of 15.5 months, the mOS for the tiragolumab + atezolizumab treatment group was 22.9 months, compared to 16.7 months for the atezolizumab monotherapy group, with an HR of 0.81 (95% CI: 0.63–1.03). The dual immunotherapy group demonstrated favorable tolerability, and no new safety signals were observed. The ARC-7 trial highlighted the capability of domvanalimab + zimberelimab to improve the prognosis of metastatic NSCLC compared to zimberelimab monotherapy [24]. However, the performance of the control group in ARC-7, which received zimberelimab, was significantly inferior to pembrolizumab. The median PFS of zimberelimab was only 5.4 months, with an ORR of 27%. In the Keynote-042 [32] and Keynote-024 [33] studies, pembrolizumab had a PFS of 6.9 months and 10.3 months, with an ORR of 39% and 45%, respectively. Therefore, it remained uncertain whether the combination therapy in ARC-7 could demonstrate such an advantage compared to pembrolizumab. The KeyVibe-001 study demonstrated that the combination of vibostolimab and pembrolizumab had certain anti-tumor efficacy and good tolerability in advanced solid tumors, including NSCLC [34]. However, the latest results from the KeyVibe-002 study of Merck indicated that vibostolimab + pembrolizumab treatment did not exhibit significant improvement in PFS in comparison to docetaxel treatment [35].

According to our NMA, anti-PD-1/PD-L1 + anti-TIGIT treatment demonstrated promising outcomes in NSCLC. Additionally, despite not significantly reducing the occurrence of TRAEs compared to chemotherapy and ICI monotherapy, anti-PD-1/PD-L1 + anti-TIGIT treatment exhibited a lower rate of grade ≥3 TRAEs (Figs. 8 and 9). Therefore, considering the performance of the aforementioned studies, we believe that tiragolumab + atezolizumab treatment holds the greatest potential for translation into clinical practice and approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the future. However, further establishment of the efficacy and safety is still needed. In terms of the target population, most clinical trials have selected individuals with high PD-L1 expression, potentially overlooking the TIGIT expression status to some extent. This oversight may ultimately impact the effectiveness of the drugs. The inhibition of TIGIT and PD-1/PD-L1 can weaken tumor immune evasion, but the complete restoration of T cell and natural killer (NK) cell activation pathways necessitates further research for validation.

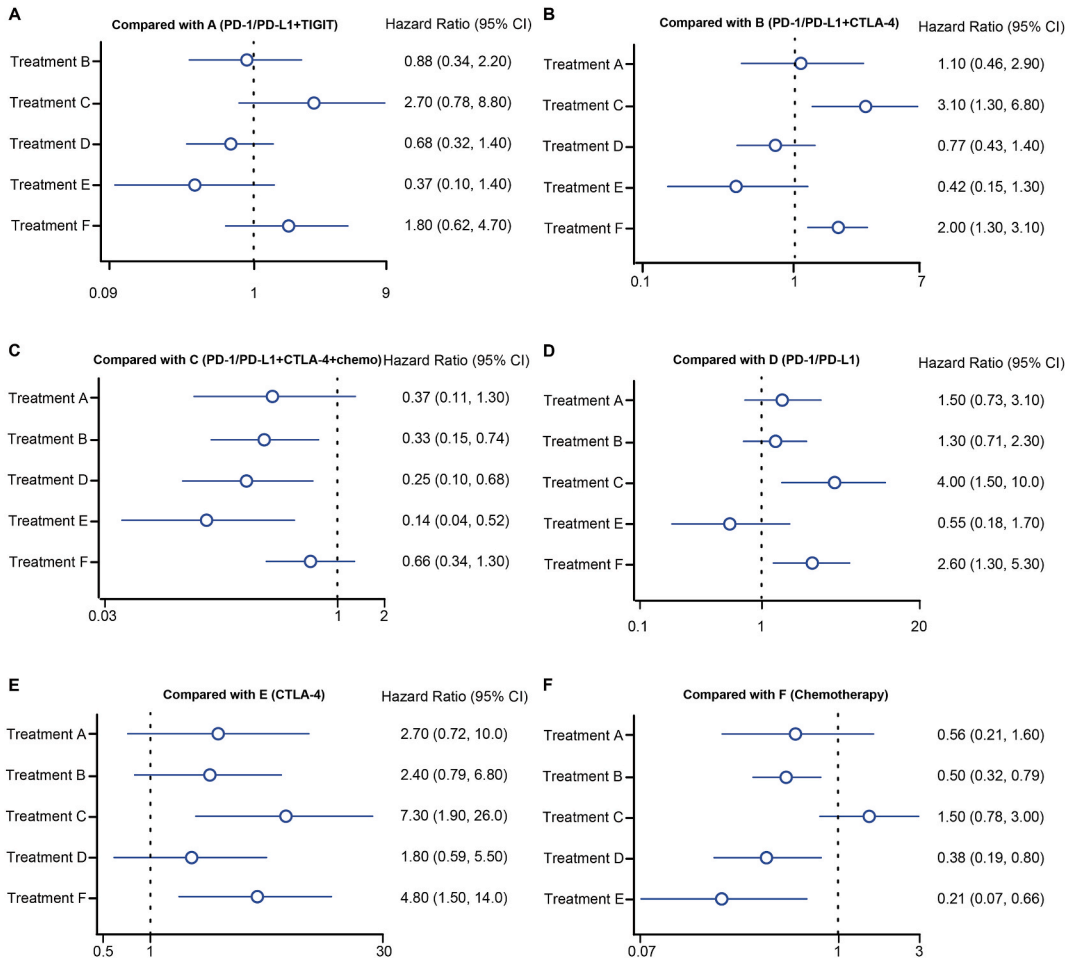

Fig. 8. Forest plots of the relative effects of TRAEs for all grades. The meaning of Treatment A-F is as described above.

Among all the dual immunotherapy regimens, anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment and anti-PD-1/PD-L1 + anti-CTLA-4 treatment ranked second and third, respectively. PD-1/PD-L1 inhibitors and CTLA-4 inhibitors regulate distinct stages of T cell activation [36]. When used in combination, they exhibit the capacity to enhance both the quantity and activity of active effector T cells [37,38]. Common treatment regimens include nivolumab + ipilimumab, pembrolizumab + ipilimumab, durvalumab + tremelimumab, among others. Several large-scale clinical studies such as CheckMate 227 and CheckMate 9LA have demonstrated significant efficacy and manageable safety of both nivolumab + ipilimumab and nivolumab + ipilimumab + chemotherapy [13,26,29,39]. Joshua E. Reuss et al. demonstrated that neoadjuvant nivolumab + ipilimumab therapy in resectable NSCLC patients, who achieved a pathological complete response (pCR), showed encouraging long-term disease-free status. However, the research was concluded prematurely due to toxic effects [40]. Additionally, compared to chemotherapy, most clinical trials investigating durvalumab + tremelimumab in advanced NSCLC did not demonstrate a significant enhancement in patient survival [15–17]. Therefore, durvalumab + tremelimumab combining with other therapies are actively being explored. The POSEIDON study suggested that for metastatic NSCLC, durvalumab + tremelimumab + chemotherapy had superior efficacy as first-line treatment compared to durvalumab + chemotherapy or chemotherapy [18]. Schoenfeld et al. investigated the treatment of ICI-resistant NSCLC using combination therapy of dual immunotherapy and radiotherapy [41]. They found that the addition of radiotherapy did not increase patients' response to durvalumab + tremelimumab therapy. In summary, the current evidence does not support a survival benefit from durvalumab + tremelimumab treatment for advanced NSCLC patients. Considering that our NMA revealed a suboptimal safety profile for anti-PD-1/PD-L1 + anti-CTLA-4 + chemotherapy treatment, further investigation is warranted to ascertain the optimal clinical application. The differential efficacy among different drug combinations may be attributed to distinct drug mechanisms and the immune microenvironment, necessitating additional exploration and research.

In addition, several emerging dual immunotherapy regimens are under investigation in clinical trials. LAG-3 and PD-1 can collaboratively regulate T cell function to facilitate tumor immune escape [42]. Preclinical study has shown that in the EG7 lymphoma mouse model, LAG-3 inhibitor plus PD-1 inhibitor resulted in 100% tumor clearance, compared to only 50% clearance with PD-1 inhibitor alone [43], suggesting a potential synergistic anti-tumor effect between PD-1 and LAG-3 inhibitors. The TACTI-002 study

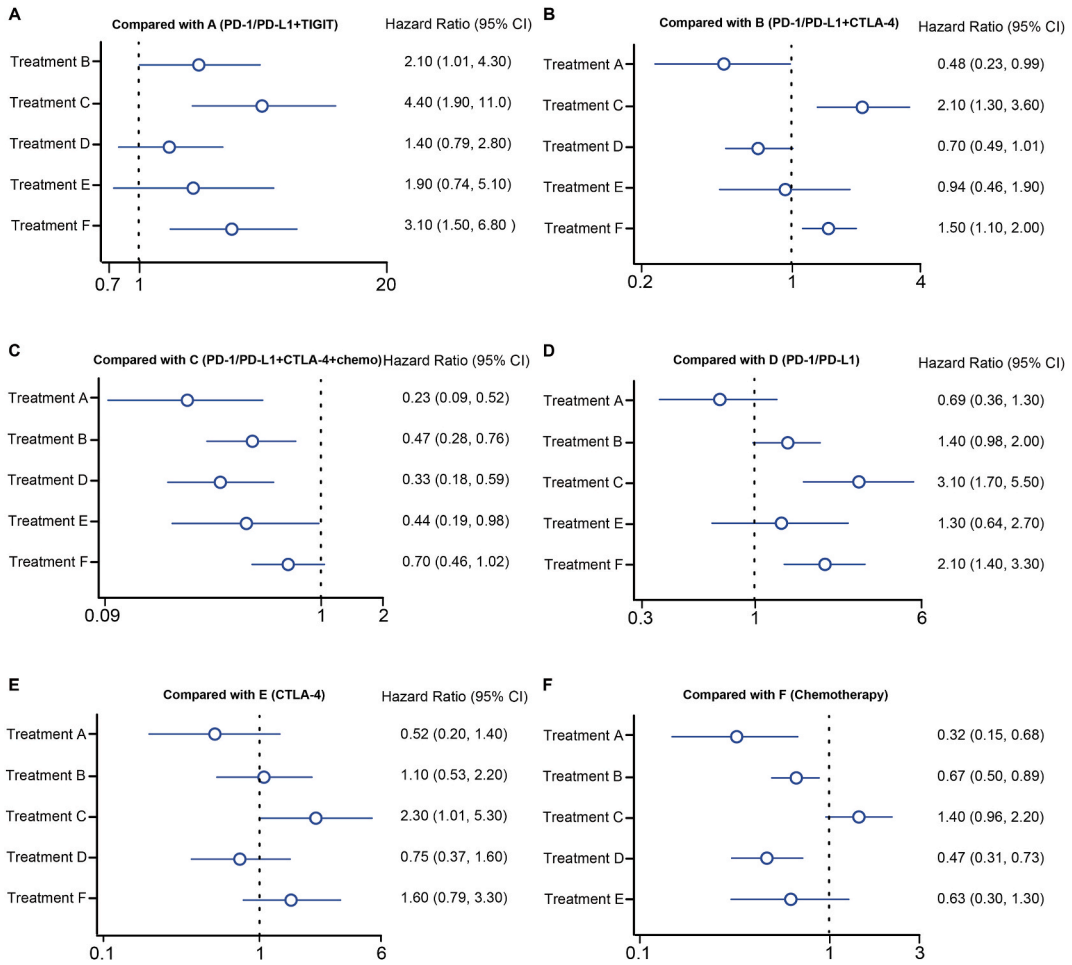

Fig. 9. Forest plots of the relative effects of grade ≥3 TRAEs. The meaning of Treatment A-F is as described above.

[44–46] revealed that eftilagimod alpha + pembrolizumab treatment for NSCLC was safe and had effective anti-tumor activity compared to pembrolizumab treatment in KEYNOTE-042 [32], warranting further investigation. A research conducted by Patrick Schöffski et al. proved that in patients with advanced malignancies, spartalizumab (anti-PD-L1) + ieramilimab (anti-LAG-3) had good tolerability, acceptable toxicity, and moderate anti-tumor activity [47]. Besides, the RELATIVITY-047 study and a clinical study (NCT02519322) has demonstrated the efficacy and safety of nivolumab + relatlimab, respectively in the treatment of unresectable or metastatic melanoma [48], and the neoadjuvant treatment of resectable melanoma [49]. Futhermore, Yun Hu et al. discovered that nanoparticle-mediated immunoradiotherapy combined with dual blockade of LAG-3 and TIGIT improved the treatment efficacy against anti-PD-1 resistant lung cancer in a murine model [50].

TIM-3, the immune checkpoint molecule within the tumor microenvironment, regulates the exhaustion of T cells and NK cells, along with modulating the inherent immune escape mediated by macrophages and dendritic cells [51,52]. An exploratory phase I/II study has affirmed the well-tolerated combination of sabatolimab (anti-TIM-3) plus spartalizumab (anti-PD-1), exhibiting initial indications of anti-tumor activity [53]. Recent research findings have unveiled that ML-T7, a small molecule targeting TIM-3, not only directly inhibits tumor progression in mice but also exhibits synergistic effects when combined with PD-1 inhibitors [54].

Interleukin (IL) inhibitor is also one of the extensively researched immunotherapeutic approach in recent years. Preclinical study has provided evidence that IL-1β inhibitors combined with PD-L1 inhibitors can synergistically inhibit tumor progression, surpassing the efficacy of monotherapy [55]. However, the CANOPY-1 trial, which evaluated the IL-1β inhibitor canakinumab combined with the PD-L1 inhibitor pembrolizumab plus platinum-based chemotherapy as first-line treatment, did not achieve the primary endpoints of improving OS and PFS in locally advanced or metastatic NSCLC [56]. Another study demonstrated that by activating NADPH oxidase 4 (NOX4), the signaling pathway involving transcription factor YY1, IL-8 and PD-L1 was sequentially activated, subsequently inducing resistance to EGFR-Tyrosine Kinase Inhibitors (TKIs) [57]. These molecules may serve as potential novel biomarkers and therapeutic targets for overcoming resistance to EGFR-TKIs in NSCLC in the future.

Bispecific antibodies (bsAbs) targeting dual immune checkpoints have demonstrated remarkable efficacy in NSCLC treatment. Currently investigated drugs include Cadonilimab, KN046, SHR-1701, and others. Cadonilimab concurrently inhibits the PD-1 and

CTLA-4 immune checkpoints, indirectly stimulating immune cells to augment the anti-tumor effect [58]. AK104-202 study disclosed that, in previously treated metastatic advanced NSCLC, cadonilimab monotherapy exhibited limited efficacy in patients with immunotherapy failure, particularly in instances of primary resistance [59]. 2023 ESMO conference announced the research findings of anti-PD-L1/CTLA-4 bsAb KN046. KN046 demonstrated good safety, significant efficacy and prolonged survival for patients with metastatic NSCLC who had previously failed EGFR-TKIs [60] or immunotherapy [61]. Additionally, KN046 combined with axitinib demonstrated encouraging efficacy and safety as first-line treatment for locally advanced or metastatic NSCLC patients with PD-L1 tumor proportion score (TPS) $\geq$ 1% [62]. SHR-1701 is a bsAb targeting transforming growth factor (TGF)-β and PD-1/PD-L1 pathway. Preclinical study has affirmed that compromised lymphocyte recovery in mice, following treatment with anti-PD-1/PD-L1 antibodies, can be restored by SHR-1701 [63]. This intervention enhanced Interferon (IFN)-γ production in $CD8^+$ T cells, exhibited stronger anti-tumor efficacy, and effectively prolonged the survival of mice. The results of a phase I clinical trial on SHR-1701 in the treatment of advanced NSCLC demonstrated promising effectiveness and safety across 3 cohorts, patients with PD-L1 positivity, EGFR-TKIs resistance, and prior PD-(L)1 treatment failure [64]. In summary, bsAbs targeting dual inhibitory checkpoints hold vast potential in NSCLC. However, their efficacy, safety, and treatment protocols still require thorough exploration in large-scale clinical trials.

So far, the population benefiting from immunotherapy in the field of lung cancer is continuously increasing, yet an ideal biomarker that accurately predicts treatment efficacy or identifies the optimal beneficiaries has not emerged. PD-L1 remains to be the currently recognized predictive biomarker for immunotherapy. However, the results from CheckMate 227 [26] and CheckMate 9LA [29] trials indicated that regardless of PD-L1 expression, dual immunotherapy alone or combined with chemotherapy had better survival outcomes in comparison to chemotherapy. Therefore, relying solely on PD-L1 expression might not provide a comprehensive or independent biomarker for predicting the efficacy of dual immunotherapy. The involvement of other immune checkpoints, such as CTLA-4, TIGIT and LAG-3, could contribute to tumor evasion mechanisms that cannot be reliably anticipated based on PD-L1 expression alone [65]. CTLA-4 methylation has been proven to predict the response and PFS in stage IV melanoma patients undergoing ipilimumab treatment [66]. TIGIT DNA hypomethylation serves as a predictive biomarker for prolonged OS and PFS in individuals receiving anti-PD-1 immunotherapy for melanoma [67]. Additionally, the expression of LAG-3 on peripheral blood cells is indicative of unfavorable outcomes in patients undergoing anti-PD-1 antibodies, anti-CTLA-4 antibodies, or a combination of both [68]. However, whether CTLA-4, TIGIT, and LAG-3 can predict the efficacy of dual immunotherapy still requires examination.

Tumor mutational burden (TMB) emerges as a potential biomarker for predicting survival benefits with immunotherapy [16, 69–71]. The MYSTIC study showed that patients with blood TMB (bTMB) $\geq$ 20 mutations per megabase (mut/Mb), treated with durvalumab and tremelimumab, demonstrated longer OS and PFS compared to chemotherapy [16]. Nevertheless, the NEPTUNE study found no association between bTMB $\geq$20 mut/Mb and clinical benefits [17]. Initial findings from the CheckMate 227 trial demonstrated that compared to chemotherapy, nivolumab plus ipilimumab yielded significantly better PFS in patients with high TMB [69], while subsequent data revealed no significant difference in survival benefits between patients with high and low TMB levels [26]. Aaron M. Goodman et al. found that elevated TMB was linked to favorable response to blockade of PD-1/PD-L1 axis in various tumors. However, the efficacy of dual checkpoint blockade did not exhibit a similarly strong correlation with TMB [72]. Thus, for dual immunotherapy, more in-depth research is imperative to explore the efficacy of TMB as a predictive biomarker.

Other potential predictive biomarkers for dual immunotherapy include CMTM6, gene inflammatory signature score, tumor-associated high endothelial venules (TA-HEVs), and the infiltration degree of $CD8^+$ T cells or tumor-infiltrating lymphocytes (TILs), among others. High co-expression of CMTM6 and PD-L1, especially within macrophages, may indicate significant benefits from PD-1 blockade in NSCLC [73]. Another research suggested that for unresectable malignant pleural mesothelioma, patients with a high score of the 4-gene inflammatory signature seemed to have better survival when treated with nivolumab plus ipilimumab [74]. Analysis of tumor biopsies from 93 patients with metastatic melanoma showed that TA-HEVs were indicative of better response and survival under anti-PD-1/PD-L1 + anti-CTLA-4 treatment [75]. Besides, preclinical study indicated that the survival benefits of dual immunotherapy were associated with $CD8^+$ T cells or TILs within the tumor [76]. Significantly higher abundance of the $EOMES^+CD69^+CD45RO^+$ effector memory T cell phenotype was observed in responders to dual immunotherapy compared to non-responders [77]. In conclusion, the search for an ideal biomarker or the establishment of a comprehensive biomarker scoring network is urgently needed. The combined application and dynamic monitoring of biomarkers may be crucial directions for future exploration.

Presently, the research focus is shifting towards the development of liquid biopsy-based biomarkers. Recent efforts aim to identify extracellular vesicle (EV)-based biomarkers linked to therapeutic response in NSCLC patients undergoing ICI treatment. Studies have predominantly concentrated on miRNAs and proteins in EVs [78]. The combination of three biomarkers, miR-199a-3p, miR-21-5p, and miR-28-5p demonstrated superior performance metrics in predicting immunotherapy response compared to PD-L1 [79]. Certain miRNAs at baseline (miR-320d, miR-320c, and miR-320b) have been specifically associated with predicting progressive disease versus partial response to ICI in NSCLC [80].

As the first NMA to investigate the efficacy of anti-PD-1/PD-L1 + anti-TIGIT regimen, our research does possess several inherent limitations. Firstly, our analysis focused solely on treatment categories and did not analyze specific drugs. Secondly, the quality of some clinical trials investigating the anti-PD-1/PD-L1 plus anti-TIGIT regimen did not meet a satisfactory level, as they were mainly phase I or II clinical trials. Additionally, two studies only provided PFS data without OS data. Thirdly, there were variations in the patient inclusion criteria among the studies included in our analysis, particularly regarding PD-L1 expression. Significantly, in three clinical trials concerning the regimen of anti-PD-1/PD-L1 + anti-TIGIT, participants were notably those with markedly elevated PD-L1 expression level. The above selective approach could potentially impact the broader applicability of the conclusion. Fourthly, we did not analyze the ORR as the relevant data were missing in some studies. Lastly, considering the restricted accessibility of clinical trial data for other dual immunotherapy regimens such as anti-PD-1/PD-L1 + anti-LAG-3 therapy and anti-PD-1/PD-L1 + anti-Tim-3

therapy, this article primarily focused on studies related to anti-PD-1/PD-L1 + anti-TIGIT and anti-PD-1/PD-L1 + anti-CTLA-4 therapies. However, despite these challenges, conducting a NMA enables us to extract valuable insights from the existing literature and establish a more robust comprehension of dual immunotherapy in NSCLC treatment.

As an emerging treatment approach, dual immunotherapy is likely to drive the exploration of novel biomarkers for accurate patient selection. Long-term clinical management of combination therapy, including treatment regimens, dose optimization, and management of adverse events, will require ongoing adjustments in clinical practice and collaboration across multiple disciplines to establish standardized protocols. Additionally, the exploration of various combination strategies involving the incorporation of novel agents and the development of new combinations with existing drugs will be important areas of future research. All these findings could inform treatment decisions and guide future research efforts aimed at optimizing the application of dual immunotherapy in the NSCLC management.

5. Conclusions

In summary, dual immunotherapy alone or combined with chemotherapy has presented superior efficacy in PFS and OS when compared to chemotherapy in advanced or metastatic NSCLC. In particular, anti-PD-1/PD-L1 antibodies combined with anti-TIGIT antibodies has exhibited encouraging outcomes in both unselected treatment line and first-line settings. In the realm of safety analysis, dual immunotherapy demonstrated a lower incidence rate of TRAEs for all grades and for grade 3 or higher compared to chemotherapy-related therapies. Besides, despite the fact that the combination of anti-PD-1/PD-L1 antibodies with anti-TIGIT antibodies did not significantly reduce the occurrence rate of TRAEs when compared to chemotherapy and ICI monotherapy, its incidence of grade $\geq$3 TRAEs was comparatively lower. Given the favorable efficacy and manageable toxicity of dual immunotherapy, we believe it holds substantial potential for widespread application in clinical practice.

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Ethics statement

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Data availability statement

Data included in article/supplementary material was presented within the article. For additional inquiries, please refer to the corresponding author.

CRediT authorship contribution statement

Yuanyuan Yang: Writing – original draft, Software, Data curation. **Dao Xin:** Writing – review & editing. **Lulu Guan:** Formal analysis, Conceptualization. **Xi Luo:** Visualization, Resources. **Han Wu:** Methodology, Investigation. **Jingwen Chu:** Validation. **Jianxiang Xing:** Supervision. **Chengjiang Liu:** Writing – review & editing, Methodology. **Feng Wang:** Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27576.

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