MEDS Clinical Medicine (2026)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2026.070106
ISSN 2616-1907 Vol. 7 Num. 1

First-Line Dual Immune Checkpoint Inhibition with PD-1/PD-L1 and CTLA-4 Blockade for Advanced Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Keywords: PD-1/PD-L1 inhibitor, CTLA-4 inhibitor, non-small-cell lung cancer, meta analysis

Abstract: Although immune checkpoint inhibitors (ICIs) have improved outcomes in non-small cell lung cancer (NSCLC), the optimal first-line combination strategy remains uncertain. This systematic review and meta-analysis evaluated the efficacy and safety of first-line PD-1/PD-L1 inhibitors in combination with CTLA-4 inhibitors for the treatment of advanced NSCLC. Five databases were searched up to September 2025, identifying ten randomized controlled trials involving 6,565 patients, which were deemed to have an overall low risk of bias. Dual immune checkpoint blockade (ICB) was found to significantly improve overall survival (OS; hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.76–0.93) compared with chemotherapy, but showed no significant benefit in progression-free survival (PFS; HR 0.96, 95% CI 0.87–1.06) or objective response rate (ORR; odds ratio [OR] 1.15, 95% CI 0.95–1.40). However, when combined with chemotherapy, CP significantly improved OS (HR 0.73, 95% CI 0.67–0.80), PFS (HR 0.70, 95% CI 0.63–0.77) and ORR (OR 1.85, 95% CI 1.53–2.23). There was a greater PFS benefit in patients with PD-L1 expression of at least 50% (HR 0.63, 95% CI 0.49–0.81). CP showed no overall differences in OS, PFS or ORR compared with PD-1/PD-L1 inhibitor monotherapy, but provided superior OS benefits in the PD-L1 <1% subgroup. Overall, there was low to moderate heterogeneity, which supports the robustness of the findings and suggests that first-line CP, particularly when combined with chemotherapy, is a feasible and promising treatment option for selected patients with advanced NSCLC.

1. Introduction

According to a recent report by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), lung cancer remains one of the most prevalent and deadly cancers worldwide [1]. According to 2025 Cancer Statistics [2], although lung cancer incidence in the United States is declining, male lung cancer mortality has fallen by 61% since its peak in 1990, while female mortality has dropped by 38% since its peak in 2002. Nevertheless, the number of

lung cancer deaths is still almost 2.5 times higher than the combined total for colorectal (2nd) and pancreatic (3rd) cancers. Lung cancer is histologically classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), with NSCLC accounting for around 87% of cases [3]. Globally, the predominant NSCLC subtype is adenocarcinoma (60–80%), followed by squamous cell carcinoma (10–20%) [4]. As early-stage NSCLC often lacks specific symptoms, presenting only with mild cough, sputum production or chest tightness, which are easily mistaken for common respiratory infections or chronic inflammation, approximately 40%-60% of patients are diagnosed at stage III–IV, missing the optimal window for curative surgery [4]. Furthermore, age-standardized five-year relative or net survival rates for lung cancer remain low in most regions (10–20%) [5], indicating a persistently poor prognosis for patients with advanced-stage disease.

The current treatment options for advanced NSCLC include chemotherapy, radiotherapy, targeted therapy and immunotherapy. Among these, immune checkpoint inhibitors (ICIs) offer notable clinical advantages. The main immunotherapy targets are CTLA-4, PD-1 and its ligand, PD-L1 [6]. PD-1 is expressed on activated immune cells, while PD-L1 is present on the cell membranes of many different types of cell. The PD-1/PD-L1 pathway suppresses excessive immune activation and maintains immune homeostasis. Blocking this interaction using PD-1/PD-L1 inhibitors removes tumour-induced immunosuppression and restores T-cell antitumour activity [7]. CTLA-4 is an early negative regulator of T-cell activation. It binds to B7 molecules (CD80/CD86) on antigen-presenting cells, competing with CD28 and thereby inhibiting T-cell activation. CTLA-4 inhibitors block this binding, thereby enhancing T-cell activation and antitumour responses [8].

Advances in immunotherapy have made dual checkpoint blockade a promising strategy for NSCLC, combining agents with complementary mechanisms to enhance anti-tumour immunity. The co-inhibition of PD-1/PD-L1 and CTLA-4 blocks immunosuppressive signals at different stages, thereby restoring T-cell activity and helping to remodel the tumour microenvironment in order to improve efficacy. Five-year results from CheckMate-227 showed that nivolumab plus ipilimumab significantly improved overall survival (OS) compared with chemotherapy across PD-L1 subgroups [9]. Similarly, the six-year follow-up of the CheckMate-9LA trial confirmed the long-term benefits of nivolumab plus ipilimumab over limited chemotherapy, regardless of PD-L1 status or histology [10]. These studies also suggest that the benefits may vary depending on PD-L1 expression, which highlights the importance of personalized treatment strategies.

Although the combination of PD-1/PD-L1 and CTLA-4 blockade shows promise, its clinical applicability is inconsistent and current guidelines offer conflicting recommendations for different patient subgroups. This meta-analysis therefore aimed to systematically evaluate the efficacy and safety of first-line PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitors for patients with advanced NSCLC. Not only does this study clarify the advantages of dual immunotherapy and immunochemotherapy over monotherapy or chemotherapy, it also conducts subgroup analyses based on PD-L1 expression levels and histological types to explore the potential for personalized treatment. Our findings aim to inform evidence-based clinical decision-making and the future optimization of immunotherapeutic strategies.

2. Materials and methods

2.1 Registration and Search Strategy

This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) 2020 statement and has been prospectively registered in the PROSPERO (CRD420251245758).

To identify all relevant studies published from database inception to September 2025, we conducted a comprehensive search of five databases: PubMed, the Cochrane Library, Embase, Web

of Science, and the China National Knowledge Infrastructure (CNKI). We used a combined strategy of subject headings and free-text terms, with search terms including 'non-small-cell lung cancer', 'PD-1/PD-L1 inhibitor', 'CTLA-4 inhibitor', and 'meta analysis'. The complete search strategies are provided in Supplementary Table S1.

2.2 Selection criteria

According to the PICOs framework, eligible studies were defined as follows: P (Population): Adult patients diagnosed with advanced (stage IIIb/IV) or metastatic NSCLC through pathological or radiological assessment and who had not previously received first-line systemic therapy. Studies could include patients with any level of PD-L1 expression, regardless of smoking history or histological subtype (squamous or non-squamous), provided they had no targetable EGFR/ALK driver mutations. I (Intervention): First-line immunotherapy involving a PD-1/PD-L1 inhibitor in combination with a CTLA-4 inhibitor. This could include PD-1 inhibitors (e.g. pembrolizumab or nivolumab), PD-L1 inhibitors (e.g. durvalumab) and CTLA-4 inhibitors (e.g. ipilimumab or tremelimumab). C (Comparison): Other first-line treatments, such as platinum-based doublet chemotherapy or single-agent chemotherapy. O (Outcomes): At least one of the following outcomes was reported: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), overall incidence of adverse events (AEs), grade ≥3 adverse events or immune-related adverse events (irAEs) [11]. S (Study design): Randomized controlled trials (RCTs).

The exclusion criteria were as follows: (1) Ineligible study design: case reports; uncontrolled case series; single-arm studies; in vitro/animal studies; review articles (used only for background information and not included in the quantitative synthesis); and conference abstracts without full data. (2) Population mismatch: studies involving populations other than NSCLC, such as small-cell lung cancer, early-stage postoperative adjuvant treatment, or trials mainly focusing on local radiotherapy. (3) Duplicate publications from the same trial.

2.3 Data extraction and quality assessment

We extracted the following data independently from each included study: the first author, the year of publication, the country, the study duration, the sample size, and the participant characteristics (including the median age, sex, NSCLC stage, histological subtype, performance status, metastatic status, and smoking history). Information on treatment regimens in the intervention groups was also recorded. We obtained antitumor efficacy outcomes (overall survival, progression-free survival, objective response rate, and disease control rate) and safety outcomes (overall adverse events, grade ≥3 adverse events, and immune-related adverse events). Subgroup analyses were performed based on PD-L1 expression, with patients categorized into four groups: negative (<1%), low (1–24%), intermediate (25–50%), and high (>50%). Additional analyses were conducted according to tissue tumor mutational burden (tTMB), treatment regimen, NSCLC stage, median age, sex, histological subtype and smoking status.

The quality of the included studies was evaluated using the Cochrane Collaboration’s Risk of Bias tool [12]. The assessment covered the following seven key domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting and (7) other sources of bias. All studies were evaluated for risk in each of these seven domains. Based on the results of this assessment, each study was classified as high, moderate or low quality.

2.4 Statistical analysis

The statistical analyses for this meta-analysis were performed using R software (version 4.5.1). For time-to-event outcomes, such as overall survival (OS) and progression-free survival (PFS), hazard ratio (HR) [13] were employed as the measure of effect. Reported HRs from individual studies were converted to their natural logarithms (log[HR]) and their corresponding standard errors were calculated for the pooled analyses. For continuous variables measured using the same methods and units, mean difference (MD) were calculated and all effect sizes were presented with 95% confidence interval (CI). The objective response rate (ORR), as a binary outcome, was analyzed using odds ratio (OR), while adverse events (AEs) were summarized using risk ratio (RR). Forest plots were generated to visually display all effect estimates. Heterogeneity was assessed using Cochran's Q test and the I^2statistic [14]. A random-effects model (DerSimonian–Laird method) was applied when $I^2 > 50\%$ or Q-test $P < 0.10$, otherwise a fixed-effects model (Mantel–Haenszel method) was used. When substantial heterogeneity ($I^2 > 50\%$) was present, predefined subgroup analyses were conducted to explore potential sources of variability. When ten or more studies were included [15], funnel plots were constructed to assess the symmetry of the study distribution. Egger's regression test and Begg's rank correlation test were then used to quantitatively evaluate publication bias. A P-value of less than 0.05 was considered statistically significant.

3. Results

3.1 Search results and patient characteristics

Figure 1 summarizes the study selection and integration process. A total of 1,788 records were initially retrieved. After removing duplicates, 1,579 records remained. Following title and abstract screening, 281 articles were excluded. Following a full-text assessment, ten RCTs were ultimately included in the meta-analysis.

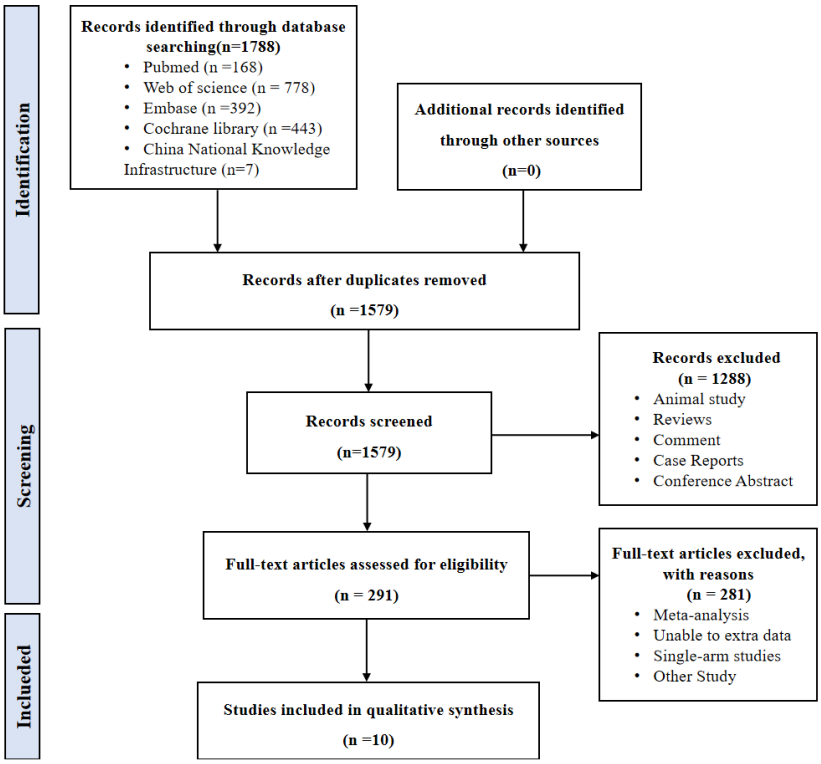

Figure 1: Flowchart of the Literature Search Strategy

A total of 10 studies [16,17,18,19,20,21,22,23,24,25] involving 6,565 patients with advanced NSCLC were included in the analysis, of whom 2,697 were female. One study enrolled patients with stage IIIB/IV disease and used a PD-L1 TC-based stratification design to divide participants into parts A and B. Among patients with PD-L1 TC <25%, four treatment groups were evaluated: CP combination therapy, C monotherapy, P monotherapy and chemotherapy. The main characteristics of the included studies, such as authors, publication year, trial name, disease stage and study duration, are presented in Table 1.

Table 1: Characteristics of Included Studies

Author (year)	Trial name	Disease stage	Study period	Group	Treatment arms	OS (95%CI)
S.Peters (2025)	POSEIDON	IV	2018-2023	Arm 1	T 75 mg q4w + D 1,500 mg q4w + chemotherapy	14.0(11.7-16.1)
				Arm 2	chemotherapy	11.6(10.5-13.1)
M.Reck (2024)	CheckMate9LA	IV	2017-2022	Arm 1	N 360 mg q3w + I 1 mg/kg q6w + chemotherapy	15.8(13.9-19.7)
				Arm 2	chemotherapy	11.0(9.5-12.7)
M.Johnson (2023)	POSEIDON	IV	2017-2021	Arm 1	T 75 mg q4w + D 1,500 mg q4w + chemotherapy	14.0(11.7-16.1)
				Arm 2	chemotherapy	11.7(10.5-13.1)
Ying Cheng (2023)	NEPTUNE	IV	2017-2018	Arm 1	D 20 mg/kg q4w + T1 mg/kg q4w	20.0(15.0-28.7)
				Arm 2	chemotherapy q3w	14.1(9.5-19.4)
N.B.Leighl (2022)	CCTG BR34	IV	2017-2018	Arm 1	D 1500 mg q3w + T 75 mg q3w + chemotherapy q3w	16.6(12.6-19.1)
				Arm 2	D 1500 mg q4w + T 75 mg q4w	14.4(10.6-18.3)
L.Paz-Ares (2021)	CheckMate9LA	IV	2017-2019	Arm 1	N 360 mg q3w + I 1 mg/kg q6w + chemotherapy	14.1(13.2-16.2)
				Arm 2	chemotherapy	10.7(9.5-12.4)
M.Boyer (2021)	KEYNOTE-598	IV	2018-2019	Arm 1	P 200mg + I 1mg/kg q6w	21.4(16.6-NA)
				Arm 2	P 200mg + placebo	21.9(18.0-NA)
N.A.Rizvi (2020)	MYSTIC	IV	2015-2016	Arm 1	D 20 mg/kg q4w	16.3(12.2-20.8)
				Arm 2※	D 20 mg/kg q4w + T 1 mg/kg q4w	11.9(9.0-17.7)
				Arm 3	chemotherapy	12.9(10.5-15.0)
D.Planchard (2020)	ARCTRC	IIIB/IV	2015-2016	PD-L1 TC ≥ 25%	Arm 1: D 10 mg/kg q2w	11.7(8.2-17.4)
					Arm 2: SOC	6.8(4.9-10.2)
				PD-L1 TC < 25%	Arm 1: D 20 mg/kg q4w + T 1 mg/kg q4w	11.5(8.7-14.1)
					Arm 2: SOC	8.7(6.5-11.7)
					Arm 3: D 10 mg/kg q2w	10.0(7.1-13.2)
					Arm 4: T 10 mg/kg q4w	6.9(3.9-13.2)
M.D.Hellmann (2019)	CheckMate227	IV	2015-2016	Arm 1	N 3 mg/kg q2w + I 1 mg/kg q6w	17.1(15.2-19.9)
				Arm 2	chemotherapy q3w	13.9(12.2-15.1)

D, durvalumab; T, tremelimumab; D + T, durvalumab + tremelimumab; P, pembrolizumab; P + I, pembrolizumab + ipilimumab; N + I, nivolumab + ipilimumab; standard treatment regimen, erlotinib, gemcitabine, or vinorelbine; NA, not available.

Arm 1 and 2※: Experimental Group Arm 2 and 3: Control Group

3.2 Risk of bias

The Cochrane Risk of Bias assessment indicated that the included studies were of moderate to high quality. Specifically, eight studies generated an adequate random sequence; ten studies

reported appropriate allocation concealment; nine studies clearly implemented participant blinding; ten studies reported blinding of outcome assessors; ten studies provided complete outcome data; nine studies showed no evidence of selective reporting; and nine studies exhibited no other sources of bias (Figure 2).

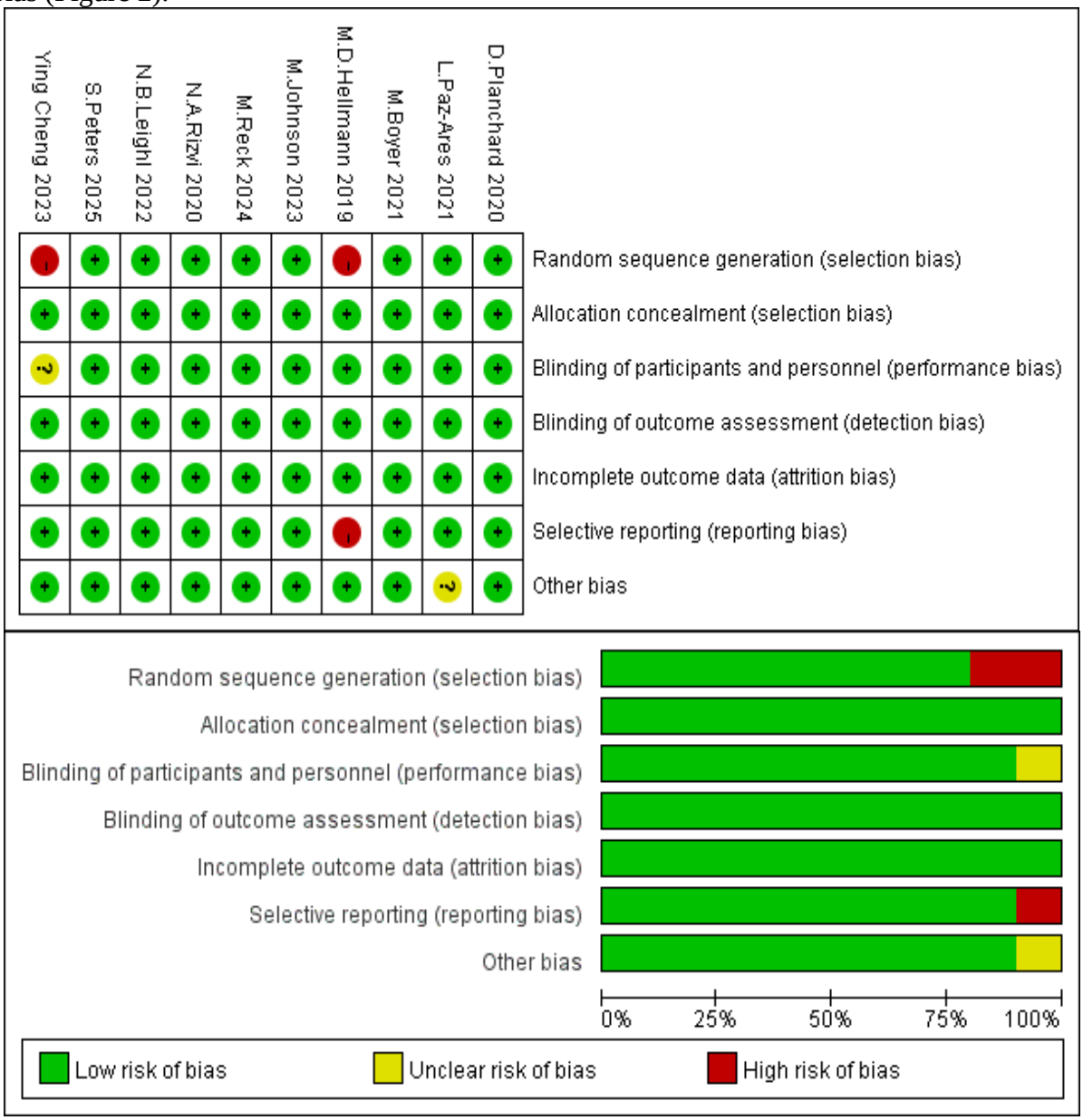

Figure 2: Risk of Bias Assessment Diagram

3.3 Overall Survival (OS)

Three studies [16,17,18] compared OS between the CP and P groups. The results revealed no significant difference in OS between the two treatment groups (MD: –0.25, 95% CI: –2.47 to 1.98). However, CP demonstrated a significant OS benefit in patients with PD-L1 <1% (MD: 4.15, 95% CI: 0.29 to 8.01) (Figure 3).

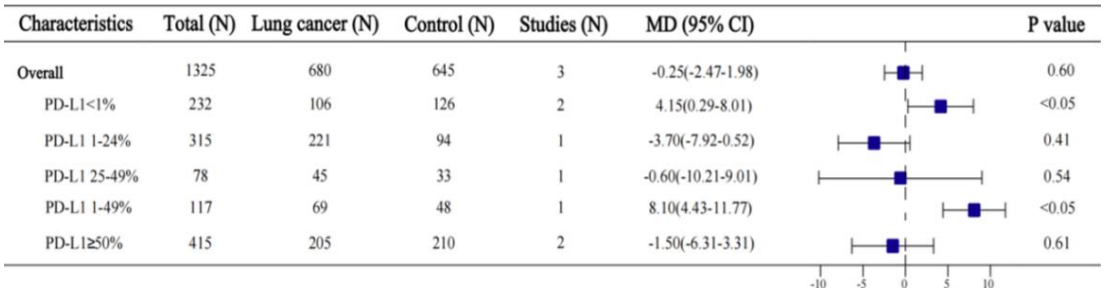

Figure 3: Forest Plot of the Meta-analysis for OS Comparing CP versus P

Four studies [17,18,19,20] compared OS between CP and chemotherapy, and another four studies [21,22,23,24] compared OS between CP plus chemotherapy and chemotherapy alone. The results indicated that CP (HR: 0.84, 95% CI: 0.76 to 0.93) and CP plus chemotherapy (HR: 0.73, 95% CI: 0.67 to 0.80) both significantly reduced the risk of death compared to chemotherapy alone. This benefit was particularly evident in patients with PD-L1 expression of less than 1% or greater than or equal to 50%, in both squamous and non-squamous histological subtypes, and in those with tTMB of greater than or equal to 10 mut/Mb. Additionally, CP plus chemotherapy outperformed CP alone in most subgroups. No significant benefit was observed in subgroups with PD-L1 = 1%, PD-L1 25–49% or tTMB <10 mut/Mb (Figure 4).

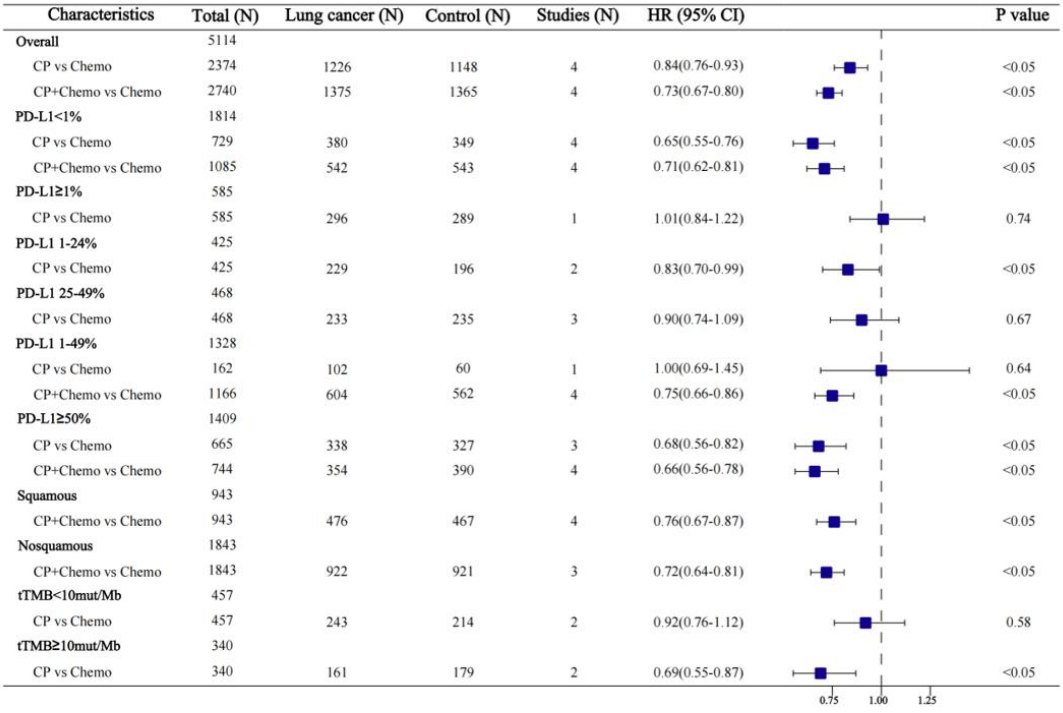

Figure 4: Forest Plot of the Meta-analysis for OS Comparing CP versus Chemotherapy and CP+Chemotherapy versus Chemotherapy

3.4 Progression-Free Survival (PFS)

Three studies [16,17,18] compared PFS between the CP and P groups. The results showed no significant difference in PFS (MD: –0.91, 95% CI: –3.19 to 1.36) (Figure 5).

Characteristics	Total (N)	Lung cancer(N)	Control (N)	Studies (N)	MD (95% CI)	P value
Overall	1563	802	761	3	-0.91(-3.19-1.36)	0.43
PD-L1<1%	106	58	48	1	1.60(-0.32-3.52)	0.51
PD-L1 1-49%	720	384	336	2	-0.69(-1.46-0.08)	0.08
PD-L1≥50%	372	188	184	1	-0.20(-3.22-2.82)	0.56

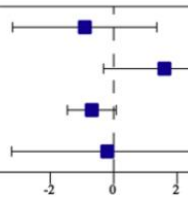

Figure 5: Forest Plot of the Meta-analysis for PFS Comparing CP versus P

Four studies [17,18,19,20] compared PFS between CP and chemotherapy, and three studies [21,22,23] compared CP plus chemotherapy with chemotherapy alone. These studies indicated that CP did not significantly improve PFS compared with chemotherapy (HR: 0.96, 95% CI: 0.87 to 1.06). However, CP plus chemotherapy was found to have a significant advantage over chemotherapy alone in terms of PFS (HR: 0.70, 95% CI: 0.63 to 0.77) (Figure 6).

Characteristics	Total (N)	Lung cancer(N)	Control (N)	Studies (N)	HR (95% CI)	P value
Overall	4439					
CP vs Chemo	2374	1226	1148	4	0.96(0.87-1.06)	0.62
CP+Chemo vs Chemo	2065	1037	1028	3	0.70(0.63-0.77)	<0.05
PD-L1<1%	1133					
CP vs Chemo	558	285	273	3	0.75(0.60-0.93)	<0.05
CP+Chemo vs Chemo	575	292	283	2	0.71(0.58-0.86)	<0.05
PD-L1≥1%	815					
CP+Chemo vs Chemo	815	407	408	2	0.69(0.59-0.81)	<0.05
PD-L1 1-49%	1395					
CP vs Chemo	928	481	447	3	0.89(0.76-1.04)	0.14
CP+Chemo vs Chemo	467	255	212	2	0.72(0.58-0.89)	<0.05
PD-L1 25-49%	10					
CP vs Chemo	10	6	4	1	0.72(0.39-1.32)	0.71
PD-L1≥50%	401					
CP vs Chemo	53	25	28	1	0.90(0.83-0.98)	<0.05
CP+Chemo vs Chemo	348	152	196	2	0.63(0.49-0.81)	<0.05

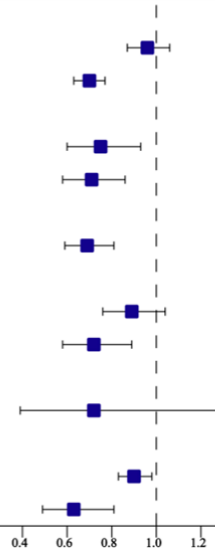

Figure 6: Forest Plot of the Meta-analysis for PFS Comparing CP versus Chemotherapy and CP+Chemotherapy versus Chemotherapy

3.5 Objective Response Rate (ORR)

Four studies [17,18,19,20] compared ORR between the CP and chemotherapy groups. Three studies [16,17,18] compared CP with P, and three studies [21,22,23] compared CP plus chemotherapy with chemotherapy alone. The results showed no significant difference in ORR for CP compared with chemotherapy (OR: 1.15, 95% CI: 0.95 to 1.40) or P monotherapy (OR: 1.03, 95% CI: 0.81 to 1.31). However, CP combined with chemotherapy significantly improved the ORR compared with chemotherapy alone (OR: 1.85, 95% CI: 1.53 to 2.23) (Figure 7).

Characteristics	Total (N)	Lung cancer (N)	Control (N)	Studies (N)	OR (95% CI)	P value
CP vs Chemo	2308	1183	1125	4	1.15(0.95−1.40)	0.45
CP vs P	1533	780	753	3	1.03(0.81−1.31)	0.73
CP+Chemo vs Chemo	2113	1060	1053	3	1.85(1.53−2.23)	<0.05

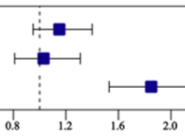

Figure 7: Forest Plot of the Meta-analysis for ORR Comparing CP vs P, CP vs Chemotherapy and CP + Chemotherapy vs Chemotherapy

3.6 Adverse events

We summarized the incidence of all-grade and grade 3–5 adverse events reported in the included studies [16-25]. In both the CP and CP plus chemotherapy groups, the most common adverse events were diarrhea and pruritus, while the most frequent grade 3–5 events were fatigue and pneumonitis (Figure 8). Compared with chemotherapy alone, the CP group showed a slightly lower incidence of all-grade adverse events (RR: 0.95, 95% CI: 0.91 to 0.98), whereas the CP plus chemotherapy group had a higher incidence (RR: 1.08, 95% CI: 1.04 to 1.13). For grade 3–5 serious adverse events, the incidence in the CP group was comparable with chemotherapy (RR: 0.95, 95% CI: 0.86 to 1.05), whereas the risk was significantly increased with CP plus chemotherapy (RR: 1.24, 95% CI: 1.12 to 1.37). Furthermore, the CP group exhibited higher rates of both all-grade (RR: 1.06, 95% CI: 1.01 to 1.12) and grade 3–5 (RR: 1.46, 95% CI: 1.28 to 1.67) adverse events compared with P monotherapy.

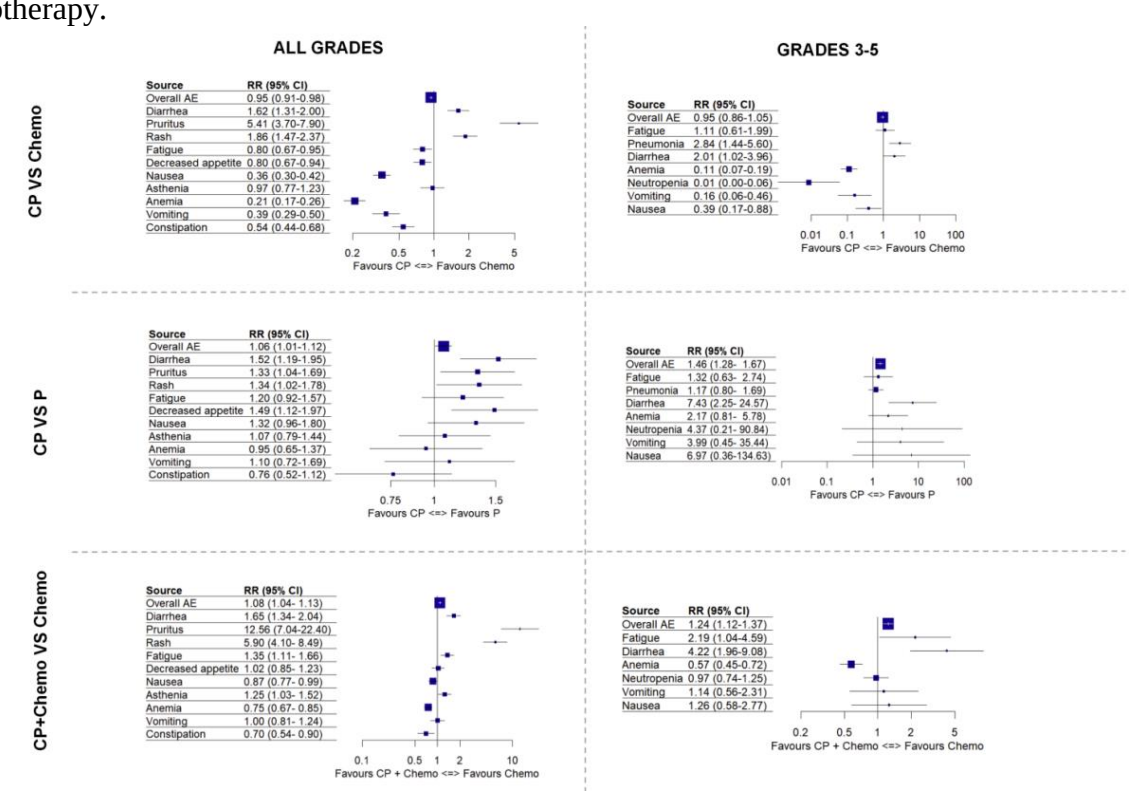

Figure 8: Forest Plot of the Meta-analysis for Adverse Events

3.7 Publication bias

This analysis, which included 10 studies, assessed publication bias for overall survival (OS). The funnel plot showed that the studies were distributed relatively symmetrically (Figure 9). Neither Egger's test (P = 0.82) nor Begg's test (P = 0.33) provided significant evidence of publication bias.

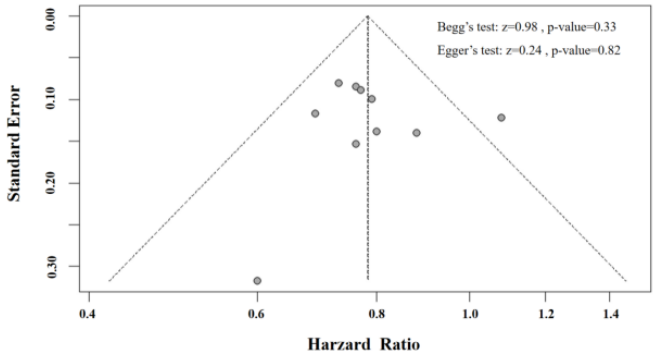

Figure 9: Funnel Plot for OS

4. Discussion

Lung cancer remains the leading cause of cancer-related death worldwide [1], with NSCLC accounting for the vast majority of cases. Despite advances in screening and treatment, the mortality rate among patients with advanced-stage disease remains high, highlighting the urgent need for more precise and effective therapeutic strategies. For advanced NSCLC without actionable driver mutations, the current first-line treatment primarily involves immune checkpoint inhibitors combined with chemotherapy [26]. However, the true clinical benefit of combining PD-1/PD-L1 inhibitors with CTLA-4 inhibitors, and the advantages this combination offers over immunotherapy or chemotherapy alone, are still being debated.

Against this backdrop, the present meta-analysis sought to systematically evaluate the efficacy and safety of first-line PD-1/PD-L1 plus CTLA-4 inhibitors in advanced NSCLC. The results showed that the triplet regimen (PD-1/PD-L1 inhibitor + CTLA-4 inhibitor + chemotherapy) significantly improved OS, PFS and ORR compared with chemotherapy alone or dual immunotherapy (PD-1/PD-L1 inhibitor + CTLA-4 inhibitor), but with a higher incidence of AEs. Dual immunotherapy significantly prolonged OS compared with chemotherapy and was well tolerated. However, dual immunotherapy showed no clear advantage over PD-1/PD-L1 monotherapy in terms of OS, PFS or ORR, and was associated with slightly higher toxicity.

This meta-analysis compares dual/triple immunotherapy with monotherapy or chemotherapy in advanced NSCLC to highlight the relative merits of different strategies.

CP versus PD-1/PD-L1 monotherapy (P) showed no significant improvement in OS, PFS or ORR in the overall population. However, CP significantly prolonged OS in the PD-L1 <1% and 1–49% subgroups, suggesting a greater benefit for patients with low PD-L1 expression. The differences from the study by Gadgeel et al. [27] are likely due to the larger pooled sample size and the heterogeneity of patient characteristics, PD-L1 distribution, chemotherapy regimens, follow-up and endpoint definitions. Compared with chemotherapy alone, CP significantly improved OS, particularly in the PD-L1 <1% and tTMB ≥10 mut/Mb subgroups. Minor discrepancies with Brahmer et al. [28] may reflect variations in dosing or treatment schedules. CP + chemotherapy significantly outperformed chemotherapy in terms of OS, PFS and ORR, with pronounced benefits observed in both the PD-L1 <1% and the ≥50% subgroups. Slight inconsistencies with Garon et al. [29] may be due to differences in the make-up of the populations and subsequent use of immunotherapy in the chemotherapy arms of the included trials.

In terms of safety, CP + chemotherapy had the highest rate of adverse events. The toxicity of CP was lower than that of chemotherapy, but higher than P. The increased toxicity of the triplet regimen is likely due to the interaction or synergistic effect between chemotherapy-induced damage to organs such as the liver, lungs and gastrointestinal tract, and immune-related toxicities. This

leads to more frequent Grade 3 and above AEs and treatment discontinuations. Overall, the combined 'dual immune activation + cytotoxic chemotherapy' effect, which drives overlapping immune, inflammatory and tissue vulnerability, is a key mechanism underlying the elevated toxicity [30].

This meta-analysis shows that CP + chemotherapy increases anti-tumour activity and significantly improves survival in patients with low immune responsiveness via synergistic mechanisms: dual checkpoint blockade increases the number of activated T cells, while chemotherapy induces immunogenic cell death and reduces the number of immunosuppressive cells (e.g. Tregs and MDSCs) [31]. Therefore, for patients with high PD-L1 expression (≥50%), the CP+ chemotherapy regimen may be the preferred option, offering superior long-term efficacy compared with chemotherapy or dual immunotherapy alone [32]. However, given its higher toxicity, proactive clinical management strategies for common or severe adverse events are essential to improve tolerability. In contrast, conventional treatments provide limited benefit for patients with low or negative PD-L1 expression [31,33]. CP offers a more balanced efficacy–safety profile, delivering better survival trends than chemotherapy or the triplet regimen, whilst reducing the risk of adverse reactions.

This study categorized patients according to their PD-L1 expression level (negative [<1%], low [1–24%], moderate [25–49%] or high [≥50%]) and their tTMB status (low [<10 mut/Mb] or high [≥10 mut/Mb]). The results showed that, in patients with PD-L1 expression of less than 1%, both CP and CP+Chemo improved OS, whereas PD-1/PD-L1 monotherapy only improved OS, with no significant benefit to PFS. In patients with high PD-L1 expression (≥50%), the triplet regimen demonstrated clear superiority to both dual immunotherapy and chemotherapy alone in terms of OS, PFS and ORR. In terms of safety, toxicity increased in the following order: PD-1/PD-L1 monotherapy < CP < chemotherapy < CP+Chemo. Thus, treatment selection can be guided by biomarker status: CP is more suitable for PD-L1-negative patients with high tTMB, offering reasonable efficacy with relatively lower toxicity. For PD-L1-high patients, the triplet regimen is preferred, provided that close monitoring of adverse events is ensured; however, dual immunotherapy remains a viable alternative when tolerability is limited.

In the absence of prospective head-to-head trials, final treatment decisions should consider patients' clinical characteristics, tolerance of toxicity and personal preferences, and involve a full discussion of the potential benefits, risks and costs of each regimen.

5. Limitation

Despite the comprehensive evidence provided, this meta-analysis has several limitations that require cautious interpretation. Firstly, only ten trials were included and the overall sample size was small, which may reduce the precision of the pooled estimates. Nevertheless, compared with previous meta-analyses, this study incorporated larger sample sizes and included multicentre and multiethnic populations. Although tumour stage information was often inadequately reported, we conducted subgroup analyses based on the available data, particularly according to PD-L1 expression and tTMB status. These analyses support the potential benefits of dual immunotherapy or triple-combination strategies in patients with low PD-L1 expression or high tTMB. Furthermore, treatment regimens varied across studies in terms of drug type and dosage. Detailed dosing information was generally unavailable, which precluded direct regimen-level comparisons. However, corresponding subgroup analyses were performed to address heterogeneity.

Despite these limitations, this analysis is more comprehensive than previous reports [17,21], as it includes a greater number of recent RCTs and systematically compares three treatment strategies. This provides more individualized evidence for clinical decision-making in advanced NSCLC.

6. Conclusion

This meta-analysis demonstrates that dual immune checkpoint blockade using PD-1/PD-L1 and CTLA-4 inhibitors significantly improves survival rates in patients with advanced non-small cell lung cancer. Patients with low or negative PD-L1 expression benefit more from CP alone, whereas those with high PD-L1 expression benefit more from CP combined with chemotherapy. However, the triple regimen is associated with higher toxicity, which limits its broader use. Overall, CP offers a more favourable balance between efficacy and safety. Further large-scale randomized trials with longer follow-up periods are needed to confirm these findings and inform precision treatment strategies.

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Supplementary Table

Table S1 Using Pubmed as an example, the retrieval process is detailed in the table below.

SET	QUERY
#1	Non-Small-Cell Lung Carcinomas[Title/Abstract]
#2	Non-Small-Cell Lung Carcinoma[Title/Abstract]
#3	Non Small Cell Lung Carcinoma[Title/Abstract]
#4	Non-Small Cell Lung Carcinoma[Title/Abstract]
#5	Non-Small Cell Lung Cancer[Title/Abstract]
#6	Non small Cell Lung Cancer[Title/Abstract]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	PD-L1 inhibit[Title/Abstract]
#9	PD-L1 Inhibitors[Title/Abstract]
#10	PD L1 Inhibitors[Title/Abstract]
#11	PD-L1 Inhibitor[Title/Abstract]
#12	PD L1 Inhibitor[Title/Abstract]
#13	Programmed Death-Ligand 1 Inhibitors[Title/Abstract]
#14	Programmed Death Ligand 1 Inhibitors[Title/Abstract]
#15	Atezolizumab[Title/Abstract]
#16	Durvalumab[Title/Abstract]
#17	Avelumab[Title/Abstract]
#18	PD-1 Inhibitors[Title/Abstract]
#19	PD 1 Inhibitors[Title/Abstract]

#20	PD-1 Inhibitor[Title/Abstract]
#21	PD 1 Inhibitor[Title/Abstract]
#22	Programmed Cell Death Protein 1 Inhibitor[Title/Abstract]
#23	Programmed Cell Death Protein 1 Inhibitor[Title/Abstract]
#24	Nivolumab[Title/Abstract]
#25	Pembrolizumab[Title/Abstract]
#26	Toripalimab[Title/Abstract]
#27	Tislelizumab[Title/Abstract]
#28	Camrelizumab[Title/Abstract]
#29	GLS-010[Title/Abstract]
#30	Cemiplimab[Title/Abstract]
#31	Sintilimab[Title/Abstract]
#32	Zimberelimab[Title/Abstract]
#33	Prolgolimab[Title/Abstract]
#34	Dostarlimab[Title/Abstract]
#35	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
#36	CTLA-4 Inhibitors[Title/Abstract]
#37	CTLA 4 Inhibitors[Title/Abstract]
#38	CTLA-4 Inhibitor[Title/Abstract]
#39	CTLA 4 Inhibitor[Title/Abstract]
#40	Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitors[Title/Abstract]
#41	Cytotoxic T Lymphocyte Associated Protein 4 Inhibitors[Title/Abstract]
#42	Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitor[Title/Abstract]
#43	Cytotoxic T Lymphocyte Associated Protein 4 Inhibitor[Title/Abstract]
#44	Ipilimumab[Title/Abstract]
#45	Tremelimumab[Title/Abstract]
#46	IB-310[Title/Abstract]
#47	XTX-101[Title/Abstract]
#48	BMS-986249[Title/Abstract]
#49	Quavonlimab[Title/Abstract]
#50	AGEN-1181[Title/Abstract]
#51	YH-001[Title/Abstract]
#52	Zalifrelimab[Title/Abstract]
#53	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
#54	randomized controlled trial [pt]
#55	controlled clinical trial [pt]
#56	randomized [tiab]
#57	placebo [tiab]
#58	clinical trials as topic [mesh:noexp]
#59	#54 OR #55 OR #56 OR #57 OR #58
#60	#7 AND #35 AND #53 AND #59