Comparative Safety of Immune Checkpoint Inhibitors and Chemotherapy in Advanced Non-Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis

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Abstract

Backgrounds: Immune checkpoint inhibitors (ICIs) alone or in combination with chemotherapy (CT) are the standard of care for first-line therapy in metastatic non-small cell lung cancer (NSCLC) patients without actionable mutations. The safety ranking of different ICI and CT combination regimens has not been investigated. This study was aimed to provide a toxicity profile and safety ranking of different ICI and CT combination regimens.

Methods: We performed comprehensive searches of phase 2 and 3 randomized clinical trials (RCTs) comparing different ICI regimens (alone or combination) or CT for the first-line treatment of advanced NSCLC. Outcomes of interest were the cumulative incidence of any treatment-related adverse events (TRAEs), grade 3-5 TRAEs (grade 3-5), any immune-related adverse events (irAEs), and grade 3-5 irAEs (grade 3-5). Odds ratios and 95% credible intervals were calculated as summary statistics to quantify the effect of different ICI combination regimens.

Results: We included 23 RCTs from 2016 to 2021 with a total of 14,378 patients. The incidence of any TRAEs and grade 3-5 TRAEs ranked from high to low were ICI-CT (probability: 74.88%), ICI-ICI-CT (50.60%), CT alone (74.79%), ICI-ICI (98.37%), and ICI monotherapy (99.37%). Adding CT to ICI regimens resulted in a higher incidence of any grade or grade 3-5 TRAEs compared to ICI-ICI combinations or ICI monotherapy. However, ICI-ICI-CT combinations did not result in a higher incidence of TRAEs than ICI-CT combinations. For any irAEs and grade 3-5 irAEs, the ranking was ICI-ICI (probability: 97.38), ICI monotherapy (96.98%), ICI-CT (99.44%), and CT alone (99.98%). Notably, the incidence of any grade and grade 3-5 irAEs was lower when adding CT to ICI monotherapy.

Conclusion: Lack of head-to-head comparisons, these findings provide evidence for clinical decision-making when considering different ICI combination regimens for advanced NSCLC patients.

Introduction

Lung cancer remains the leading cause of cancer deaths worldwide, including in Taiwan.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases, and more than 70% of NSCLC patients present with locally advanced or metastatic disease (stage III or IV) at the initial diagnosis.[2] Immune checkpoint inhibitors (ICIs) including monoclonal antibodies targeting cytotoxic T-lymphocyte protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death ligand-1 (PD-L1), have been introduced to various cancer treatments, and they have become one of the most important therapies for patients with cancer. In addition, they have been shown to provide a higher and more durable treatment response with relatively tolerable toxicity compared to conventional chemotherapy (CT).[3, 4] Treatment with ICIs alone or in combination with CT is the standard of care for the first-line therapy of patients with metastatic NSCLC without driver gene mutations. Clinically, the selection of these different regimens is mainly based on the histological type, PD-L1 expression and outcomes from different trials.[5, 6]

The toxicity of chemotherapeutic drugs has been extensively researched and can be adequately managed based on clinical experience. However, the side effects of ICIs, especially immune-related adverse events (irAEs), are unique and can involve multiple organs with different onset patterns and severity, which are less familiar to clinicians. The incidence of grade 3-5 irAEs varies according to the ICIs used, dose, and combination regimen, ranging from 6% to 55%. These irAEs can lead to life-threatening conditions and treatment discontinuation, further compromising the outcomes.[7] Currently, both ICI monotherapy and in combination with CT are treatment options for metastatic NSCLC patients with a high PD-L1 expression. A meta-analysis found that the combination of ICIs (pembrolizumab or atezolizumab) and CT resulted in significantly better progression-free survival (PFS) and overall survival (OS) compared to pembrolizumab monotherapy in non-squamous NSCLC patients with a high PD-L1 level.[8] However, retrospective studies have demonstrated a comparable benefit in OS with these two treatment modalities.[9, 10] The combination of nivolumab plus ipilimumab with or without two cycles of platinum-doublet CT has also been approved as first-line treatment for metastatic NSCLC patients without genomic tumor mutations.[5, 6] In addition, a recent meta-analysis suggested that anti-PD-1 combinations may be associated with higher survival outcomes than PD-L1 combinations for patients with advanced NSCLC.[11] Given the multiple treatment options and inconsistent efficacy results among different combination strategies, it is important to understand the safety profiles of these regimens.

Therefore, the aim of this network meta-analysis (NMA) was to investigate the adverse events associated with ICI monotherapy or in combination with different ICIs or CT as first-line therapy for advanced NSCLC, and provide a safety ranking of these different

modalities.

Methods

Data Sources and Search Strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines.[12] We performed a literature search in PubMed, Embase, Cochrane Library, and CENTRAL records for relevant studies published up to July 1, 2021. Abstracts or presentations of international scientific conferences including the American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Society for Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC) were also checked to ensure that the most recent updated data were included. In addition, reference lists of the included studies were inspected, and experts and physicians in this field were also consulted. The project was prospectively registered in the PROSPERO database of systematic reviews (CRD42021268464).

Study Selection and Data Extraction

Studies that met the following criteria were included: (1) those that enrolled patients with treatment-naïve advanced (stage IIIB/IIIC/IV) NSCLC; (2) randomized clinical trials (RCTs) using ICI monotherapy or in combination with other ICIs or CT; and (3) phase 2 and 3 trials reporting grade 3-5 or any grade of TRAEs or irAEs according to the definitions and criteria of the recruited clinical trials.

Quality and Risk of Bias Assessment

The abstract of each study was independently assessed by three authors to confirm the eligibility for analysis. Data from the included studies were independently extracted and checked. Two reviewers independently assessed the risk of bias of the included studies according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions 5.1. Each criterion was marked as unclear, low, moderate, or high risk of bias. Disagreements were resolved by consensus or assessed by other authors.

Outcome Measurements

The outcomes of interest were grade 3-5 and any grade of TRAEs and irAEs according to the definitions used in the trials. We ranked the probability of a treatment regimen being associated with the risk of TRAEs and irAEs from highest to lowest by estimating the risk of each treatment regimen.

Data Synthesis and Statistical Analysis

Studies were pooled to determine the risk of adverse events with different treatment regimens in NMA, and quantified with odds ratios (ORs) and 95% credibility intervals (CrIs). Random effect models generating posterior distributions of model parameters were chosen to calculate ORs and 95% CrIs in a Bayesian framework, which were considered to be conservative estimations managing between-study heterogeneity.[13] On the basis of ORs, the posterior probability of being the best to the worst for each treatment regimen was provided and ranked by calculating the surface under the cumulative ranking curves. Subgroup analyses were performed based on system or organ-specific irAEs, including infusion reactions, endocrine, gastrointestinal, hepatic, respiratory, renal, and dermatologic irAEs. A two-sided p value of <0.05 was considered to be significant. The NMA was conducted using the interactive web-based software, *MetalInsight* version 3.14, powered by the *shiny* and *netmeta* packages for R.[14] All Bayesian statistical calculations were performed using R package *netmeta*[15] and *gemtc*.[16] Plots depicting the network geometry and forest plots were generated using *MetalInsight*.

To facilitate clinical translation, the number needed to benefit (NNTB) and number needed to harm (NNTH) were calculated from the overall ORs and control event rate.[17] The NNTB and NNTH calculations and Cates plots were generated at <http://www.nntonline.net/visualrx/>.

To ensure the stability and consistency of the findings, we conducted several sensitivity analyses. First, we repeated the analysis using datasets excluding each single trial one by one. Second, we used the node-splitting method to assess the consistency between direct and indirect comparisons in the NMA.[18]

Results

Study Characteristics

The search strategy is shown in **Supplementary Figure S1**. A total of 14,378 patients were included from 23 clinical trials conducted between 2016 and 2021.[19-41] The characteristics of the included studies are summarized in **Table 1**. Among these studies, 4 trials included squamous patients only, 7 studies included non-squamous patients only, and 12 included patients of both histologies. The investigated drugs were pembrolizumab in 5 trials, nivolumab in 4, atezolizumab in 5, durvalumab in 2, tislelizumab in 2, sintilimab in 2, cemiplimab in 1, camrelizumab in 1, and pembrolizumab plus nivolumab in 1. Comparative network plots are illustrated in **Figure 1**. Five different treatment regimens (ICI-CT, ICI-ICI-CT, ICI-ICI, CT alone, and ICI monotherapy) were compared for TRAEs, and 4 different treatment regimens (ICI-CT, ICI-ICI, CT alone, and ICI monotherapy) were compared for irAEs.

Risk-of-Bias Assessments

As illustrated in **Supplementary Figure S2**, all of the studies had a low risk of reporting bias. An unclear risk of performance bias was detected in 17 studies due to the open-label study design, allocation bias was detected in 4 studies due to an unequal ratio of assigned patients, and selection bias was detected in 5 studies as the study populations were from Asia or China only. A high risk of detection bias was detected in the RATIONALE 307 study due to the possibility of investigator bias, and attrition bias was detected in 2 studies (RATIONALE 304, ORIENT-12) due to a high percentage of missing data.

Outcome Assessments

Any grade and grade 3-5 TRAEs

The forest plots and results of the NMA for TRAEs are shown in **Figure 2**. Compared to CT alone, a significantly higher risk of any TRAEs was observed with ICI-CT (OR 1.63, 95% CrI 1.12 to 2.39). However, the incidence of any TRAEs was comparable between ICI-ICI-CT combinations and CT alone (OR 1.26, 95% CrI 0.62 to 2.57). Compared to CT alone, a lower incidence of TRAEs was found with ICI monotherapy (OR 0.2, 95% CrI 0.2 to 0.39) and ICI-ICI combinations (OR 0.51, 95% CrI 0.34 to 0.79) (**Figure 2A**).

A similar pattern was demonstrated for grade 3-5 TRAEs (**Figure 2B**). A higher risk of grade 3-5 TRAEs was demonstrated with ICI-CT combinations compared to CT alone (OR 1.54, 95% CrI 1.38 to 1.78), and a lower risk of grade 3-5 TRAEs was demonstrate with ICI and ICI-ICI combinations compared to CT alone (ORs 0.35 and 0.68, 95% CrI 0.29 to 0.42 and 0.53 to 0.87, respectively).

Figure 2C shows the ORs of any grade and grade 3-5 TRAEs with different treatment regimens. Compared to ICI monotherapy, CT alone and all ICI-based combinations were associated with a greater risk of any grade and grade 3-5 TRAEs. Of note, ICI-ICI-CT combinations were not associated with higher rates of all grade and grade 3-5 TRAEs compared to ICI-CT combinations or CT alone.

The ranking profiles for different regimens on the risk of any grade TRAEs showed that ICI-CT combinations were associated with the greatest risk (probability: 74.88%), followed by ICI-ICI-CT (50.60%), CT alone (74.79%), ICI-ICI (98.37%), and ICI monotherapy (99.37%) (**Figure 4A**). This order was the same for grade 3-5 TRAEs.

All grade and grade 3-5 irAEs

The forest plots for all grade and grade 3-5 irAEs are shown in **Figure 3**. A significantly higher risk of any irAEs was found with ICI monotherapy (OR, 6.47; 95% CrI 3.83-11.44), ICI-CT (OR, 2.49; 95% CrI 1.72-3.76), and ICI-ICI (OR, 12.69; 95% CrI 5.89-28.28) compared to CT alone (**Figure 3A**). As shown in **Figure 3B**, the incidence of grade 3-5 irAEs was consistent to that of all grade irAEs, with ORs of 7.94, 2.19, and 23.29, and 95% CrIs of 4.27 to 16.73, 1.57 to 3.02, and 10.45 to 56.95 for ICI monotherapy, ICI-CT, and ICI-ICI combinations, respectively, compared to CT alone.

The ORs of all grade and grade 3-5 irAEs with different treatment regimens are demonstrated in **Figure 3C**. Of note, the incidence of any grade and grade 3-5 irAEs was lower (ORs 0.39 and 0.28, 95% CrIs 0.2-0.74 and 0.12 to 0.56, respectively) with ICI-CT combinations compared to ICI monotherapy. In addition, ICI-ICI was associated with a higher risk of any grade and grade 3-5 irAEs (ORs 5.09 and 10.62, 95% CrIs 2.11-12.15 and 4.5 to 27.92, respectively) compared to ICI-CT combinations.

The ranking profiles for different regimens on the risk of any grade irAEs showed that ICI-ICI combinations were associated with the greatest risk (probability: 97.38), followed by ICI monotherapy (96.98%), ICI-CT (99.44%), and CT alone (99.98%) (**Figure 4B**). This order was similar for grade 3-5 irAEs.

Number needed to benefit (NNTB) and number needed to harm (NNTH)

The frequency and proportion of the NNTB between group comparisons and the Cates plots are illustrated in **Supplementary Figure S3**. In summary, the NNTBs were 7 (95% confidence interval [CI] 5 to 11) and 17 (95% CI 9 to 56) for ICI monotherapy and ICI-ICI to prevent a TRAE compared to the CT group, respectively. The NNTH was 37 (95% CI 25 to 136) for ICI-CT to cause a TRAE compared to CT alone. There was no significant difference in TRAE rate between ICI-ICI-CT and CT alone. For any irAEs, the NNTHs were 3 (95% CI 2 to 4) for ICI monotherapy, 5 (95% CI 4 to 9) for ICI-CT, and 2 (95% CI 2 to 3) for ICI-ICI to cause an irAE compared to CT alone (**Supplementary Figure S4**).

Subgroup analyses of system or organ-specific irAEs

The ranking probability of a treatment regimen being associated with any irAEs varied by organ or system. For all included system or organ-specific irAEs, CT alone had the lowest ranking (**Supplementary Table S1**). ICI-ICI-CT was associated with the highest risk of irAEs in endocrine, hepatic, dermatologic irAEs, and infusion reactions, whereas ICI-ICI was associated with the greatest risk of irAEs in gastrointestinal, hepatic irAEs and pneumonitis. ICI-CT was associated with the highest risk of renal irAEs.

Sensitivity analyses

The results of the analyses in which each single trial was sequentially excluded were qualitatively consistent with those without excluding any trial. The OR estimates for any TRAEs, grade 3-5 TRAEs, any irAEs, and grade 3-5 irAEs varied minimally with no change in the ranking orders of probability. In addition, according to the **node-splitting model**, similarity was observed across direct, indirect, and network comparisons, which implied no significant inconsistency (**Supplementary Table S2**).

Discussion

The results of this NMA demonstrated that ICI-CT combinations were associated with a higher incidence of any grade or grade 3-5 TRAEs compared to ICI-ICI combinations or ICI monotherapy. However, ICI-ICI-CT regimens were not associated with a higher incidence of any grade or grade 3-5 TRAEs than ICI-CT combinations. Surprisingly, the incidence of any grade and grade 3-5 irAEs was lower when CT was added to ICI monotherapy. Subgroup analysis of system or organ-specific irAEs demonstrated that the incidence of irAEs was highest for ICI-ICI-CT and ICI-ICI combinations and lowest for CT monotherapy.

Several studies have focused on comparisons and meta-analysis of first-line ICI combination regimens among patients with advanced NSCLC.[8, 11] Dafni et al reported a meta-analysis based on 12 studies with 9,236 metastatic NSCLC patients, and concluded that the addition of CT to ICIs enhanced their treatment efficacy as first-line treatment for advanced NSCLC.[8] In terms of toxicity, no significant difference in the incidence of any grade ≥ 3 adverse event was observed between pembrolizumab/CT and CT alone, while a higher incidence of TRAEs was observed with atezolizumab/CT and ipilimumab/CT. In addition, the incidence of TRAEs with ICI-ICI combinations was lower compared to CT alone, and all ICI monotherapies were associated with a significantly lower incidence of TRAEs compared to CT alone. These results are in concordance with the current study. However, the incidence of irAEs was not specified in their study. In the current study, we found that the incidence of any grade and grade 3-5 irAEs was highest with ICI-ICI combinations followed by ICI monotherapy, and that adding CT to ICI monotherapy reduced the incidence of ICI-related irAEs. Another meta-analysis conducted by Liu et al analyzed 16 studies with 10 ICI combinations and 8,278 advanced NSCLC patients.[11] The safety results indicated that the addition of CT to ICIs increased treatment-related toxicities compared to standard CT, and the authors concluded that toxicity was lowest for the ICI-ICI combinations across all combination treatments. Similarly, their study did not specify the irAEs with different combination treatments. Their subgroup analysis suggested that nivolumab plus ipilimumab plus CT was associated with the best OS in patients with a PD-L1 expression $<1\%$, and that pembrolizumab plus chemotherapy was associated with the best OS in patients with a PD-L1 expression $\geq 1\%$. However, the incidence of irAEs with different treatment regimens should be taken into consideration, because most clinicians are more familiar with CT-related toxicities rather than irAEs. Although ICI-containing regimens increase the incidence of irAEs, adding CT to ICI monotherapy may decrease the incidence of irAEs. Recently, Berti et al included 16 ICI trials in a meta-analysis and reported rates of any grade irAEs and severe irAEs

with ICIs of 37.1% and 18.5%, respectively.[42] Pooled analysis on any, severe and organ-specific irAEs showed that ICI monotherapy was associated with a significantly lower risk of irAEs compared to immuno-chemotherapy.[42] These results are in contrast to those of the present study. A possible explanation is the heterogeneity of the included studies. The enrolled trials in the current study all investigated first-line NSCLC treatment, whereas Berti's report enrolled 4 second-line treatment trials, 1 maintenance treatment trial, and 2 small cell lung cancer treatment trials. In addition, the recruited number of patients was smaller than in the present study.

The development of irAEs can affect various organs with different clinical symptoms such as endocrine (hyperthyroidism, hypothyroidism, and adrenal insufficiency), dermatological (rash and pruritus), gastrointestinal (diarrhea and colitis), hepatic (hepatitis), respiratory (pneumonitis), and kidney (renal insufficiency) symptoms. System and organ-specific analyses in the current study indicated that the incidence of irAEs was highest with ICI-ICI-CT and ICI-ICI combinations, followed by ICI monotherapy, ICI-CT, and CT alone in endocrine, dermatologic, hepatic, and respiratory-related irAEs. Pneumonitis is a clinically relevant and potentially life-threatening irAE, and a previous meta-analysis reported that its incidence may be higher with PD-1 inhibitors than PD-L1 inhibitors, and that the incidence was highest with ICI-ICI combinations.[43] However, detailed comparisons between different ICI treatment-related risk profiles for organ-specific irAEs are lacking. **Several studies have indicated that the development of irAEs after ICI treatment was associated with a better response and survival.[44, 45] However, this association may be biased by differences in histological subtype, disease burden, and lines of treatment. We focused our analyses on TRAEs and irAEs with ICIs, providing detailed data for clinicians which will be helpful when choosing different treatment regimens with regards to both efficacy and safety.**

The strength of this study is that it is the first NMA to thoroughly examine the risk of irAEs with different ICI combination regimens in currently available trials as first-line treatment for advanced NSCLC. In addition, we provided risk profiles including ranking, NNTB and NNTH of different ICI combination regimens to improve clinical decision making for treatment strategies. There are several limitations to this study. First, the reported criteria for TRAEs and irAEs in the included RCTs were not exactly the same. Therefore, we analyzed system or organ-specific irAEs to minimize heterogeneity. Second, we did not conduct subgroup analyses on the basis of histologic types, PD-L1 expression, ICI types, or individual ICI and CT drugs to identify possible differences in the toxicities of these specific populations or medications. Finally, the median follow-up time was different for all included studies, ranging from 8.0 to 59.9 months. Awareness and reporting of TRAEs and irAEs may have increased over time, and thus reporting bias may have existed.

In conclusion, this NMA demonstrated that ICI-CT combinations were associated with a higher incidence of any grade or grade 3-5 TRAEs compared to ICI-ICI combinations or ICI monotherapy. However, ICI-ICI-CT combinations were not associated with a higher incidence of any grade or grade 3-5 TRAEs than ICI-CT combinations. Importantly, the incidence of any grade and grade 3-5 irAEs was lower when CT was added to ICI monotherapy. Subgroup analysis of system or organ-specific irAEs demonstrated that the incidence of irAEs ranked from high to low for ICI-ICI, ICI monotherapy, ICI-CT, and CT alone in terms of endocrine, hepatic, dermatologic, and respiratory-related irAEs. These findings provide evidence for clinicians on the efficacy and safety of different ICI combination regimens for advanced NSCLC patients.

Abbreviations

CT = chemotherapy; CTLA-4 = cytotoxic T-lymphocyte protein-4; CrIs = **credibility intervals**; ICIs = immune checkpoint inhibitors; irAEs = immune-related adverse events; NSCLC = non-small cell lung cancer; NMA = network meta-analysis; NNTB = number needed to benefit; NNTH = number needed to harm; ORs = odds ratios; PD-1 = programmed cell death protein-1; PD-L1 = programmed death ligand-1; TRAEs = treatment-related adverse events

Declarations

Ethics approval and consent to participate: This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication: Not applicable

Availability of data and material: The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

Competing interests: All authors (C.-Y. Chen., C.-H. Huang, W.-C. Chen, M.-S. Huang, and Y.-F. Wei) have no conflicts of interest to disclose

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Tables

Table 1. Characteristics of the included studies

No.	Study (year)[Ref.]	Phase	Histology	N	PD-L1 expression	Therapy	Median follow-up (months)	ORR (%)	mPFS (months)	mOS (months)
1	Awad et al. (2021), KN021	2	non-squamous NSCLC	60	ALL	Pembrolizumab plus CT	49.4	58	24.5	34.5
				63		CT		33	9.9	21.1
2	Reck et al. (2019)*, KN024	3	NSCLC	154	≥50%	Pembrolizumab	59.9	46.1	7.7	26.3
				151		CT		31.1	5.5	13.4
3	Mok et al. (2019)*, KN042	3	NSCLC	637	≥1%	Pembrolizumab	46.9	27.3	5.5	16.4
				637		CT		26.7	6.8	12.1
4	Gadgeel et al. (2020), KN189	3	non-squamous NSCLC	410	≥1%	Pembrolizumab plus CT	23.1	47.6	9.0	22.0
				206		CT		18.9	4.9	10.7
5	Paz-Ares et al.(2020), KN407	3	Squamous NSCLC	278	ALL	Pembrolizumab plus CT	14.3	62.6	8.0	17.1
				281		CT		38.4	5.1	11.6
6	Carbone et al.(2017), CM026	3	NSCLC	271	≥5%	Nivolumab	13.5	26	4.2	14.4
				270		CT		33	5.9	13.2
7	Hellmann et al. (2019)**, CM227	3	NSCLC	391	≥1%	Nivolumab plus Ipilimumab	54.8	35.9	5.1	17.1
				391		Nivolumab		27.5	4.2	15.7
				387		CT		30	5.6	14.9
				185	<1%	Nivolumab plus Ipilimumab	54.8	27.3	5.1	17.2
				172		Nivolumab		37.9	5.6	15.2
				183		CT		23.1	4.7	12.2
8	Sugawara et al. (2021), TASUKI-52	3	NSCLC	275	ALL	Nivolumab plus CT	13.7	61.5	12.1	25.4
				275		CT		50.5	8.1	24.7
9	Paz-Ares et al. (2021)**, CM 9LA	3	NSCLC	361	ALL	Nivolumab plus Ipilimumab plus CT	30.7	38.0	6.7	15.8
				358		CT		25.4	5.2	11.0
10	West et al. (2019), IMP 130	3	non-squamous NSCLC	483	ALL	Atezolizumab plus CT	18.5	49.2	7.0	18.6
				240		CT	19.2	31.9	5.5	13.9
11	Jott et al. (2020), IMP 131	3	Squamous NSCLC	338	ALL	Atezolizumab plus CT (CP)	NA	NA	NA	NA
				343		Atezolizumab plus CT (CnP)	26.8	59.4	6.3	14.2
				340		CT (CnP)	24.8	51.3	5.6	13.5

12	Jassem et al.(2021), IMP 110	3	NSCLC	286	ALL	Atezolizumab	31.3	31.4	5.8	18.9
				263		CT		32.1	5.6	14.7
13	Reck et al. (2019), IMP 150***	3	NSCLC	402	ALL	Atezolizumab plus CT	39.8	40	6.9	19.0
				400		Atezolizumab plus Bevacizumab plus CT		56	8.3	19.8
				400		Bevacizumab plus CT		41	6.8	15.0
14	Nishio et al. (2020), IMP 132	3	non-squamous NSCLC	292	ALL	Atezolizumab plus CT	28.4	47	7.7	17.5
				286		CT		32	5.2	13.6
15	Rizvi et al. (2020), MYSTIC	3	NSCLC	163	ALL ($\geq 25\%$)	Durvalumab	30.2	35.3	4.7	16.3
				163		Durvalumab plus Tremelimumab		34.4	3.9	11.9
				162		CT		37.7	5.4	12.9
16	Leighl et al. (2020), CCTG BR-34	3	NSCLC	151	ALL	Durvalumab plus Tremelimumab plus CT	24	23.6	7.7	16.6
				150		Durvalumab plus Tremelimumab		14.1	3.2	14.1
17	Sezer et al. (2021), EMPOWER-Lung 1	3	NSCLC	355	$\geq 50\%$	Cemiplimab	13.1	39	9.6	18.9
				342		CT		20	6.0	15.8
18	Boyer et al. (2021), KN598	3	NSCLC	284	$\geq 50\%$	Pembrolizumab-Ipilimumab	20.6	45.4	8.2	21.4
				284		Pembrolizumab		45.4	8.4	21.9
19	Zhou et al. (2021), Camel	3	non-squamous NSCLC	205	All	Camrelizumab plus CT	19.3	60.5	11.3	NR
				207		CT		38.6	8.3	20.9
20	Yang et al. (2020), ORIENT-11	3	non-squamous NSCLC	266	All	Sintilimab plus CT	8.9	51.9	8.9	NR
				131		CT		29.8	5.0	NR
21	Zhou et al. (2021), ORIENT-12	3	Squamous NSCLC	179	ALL	Sintilimab plus CT	8.0	NA	5.1	NR
				178		CT		NA	4.9	NR
22	Lu et al. (2021), RATIONALE 304	3	non-squamous NSCLC	223	All	Tislelizumab plus CT	9.8	57.4	9.7	NR
				111		CT		36.9	7.9	NR
23	Wang et al. (2021), RATIONALE 307	3	Squamous NSCLC	120	ALL	Tislelizumab plus CT (CP)	8.6	72.5	7.6	NA
				118		Tislelizumab plus CT (CnP)		74.8	7.6	NA

	117	CT (CP)	49.6	5.5	NA

CT = chemotherapy; CP = carboplatin plus paclitaxel; CnP = carboplatin plus nab-paclitaxel; mOS = median overall survival; mPFS = median progression-free survival; NA = not applicable; NR = not reached; ORR = objective response rate; PD-L1 = programmed death ligand-1

*updated data in the 2020 ESMO meeting; **updated data in the 2021 ASCO meeting; ***updated data in the 2020 AACR meeting

Figures

A

B

Figure 1

Comparative Network Diagram for TRAEs (a) and irAEs (b) of five different treatment regimens for advanced NSCLC in 23 trials. Circular nodes represent treatment regimens. The size of each circle indicates the number of cases. The colors represent the different treatment regimens. The width of the lines and the numbers next to these lines indicate the number of studies.

Figure 2

<p>Risk of any TRAEs and grade 3-5 TRAEs associated with each treatment combination regimen.Forest plots of any TRAEs and grade 3-5 TRAEs for different treatment regimens compared with CT alone are shown in (A) and (B), respectively. Figure 2C shows the risk of any TRAEs (blue background) and grade 3-5 TRAEs (pink background) of each comparison among all treatment regimens.The pooled odds ratios (95% credible intervals) were the results of comparing the right column treatment regimens with the left column treatment regimens (the reference group).Bold text indicates statistical significance at p<0.05.</p>

C.

CT alone	6.47 (3.83, 11.44)	2.49 (1.72, 3.76)	12.69 (5.89, 28.28)
7.94 (4.27, 16.73)	ICI	0.39 (0.2, 0.74)	1.96 (0.99, 3.79)
2.19 (1.57, 3.02)	0.28 (0.12, 0.56)	ICI-CT	5.09 (2.11, 12.15)
23.29 (10.45, 56.95)	2.92 (1.64, 5.1)	10.62 (4.5, 27.92)	ICI-ICI

Figure 3

<p>Risk of any grade and grade 3-5 irAEs associated with different treatment regimens. Forest plots of any irAEs and grade 3-5 irAEs for different treatment regimens compared with CT alone are shown in (A) and (B), respectively. Figure 3C shows the risk of any irAEs (blue background) and grade 3-5 irAEs (pink background) of each comparison among all treatment regimens. The pooled odds ratios (95% credible intervals) were the results of comparing the right column treatment regimens with the left column treatment regimens (the reference group). Bold text indicates statistical significance at p<0.05.</p>

Figure 4

<p>Ranking profiles for the different treatment regimens on any TRAEs and grade 3-5 TRAEs (A) and on any irAEs and grade 3-5 irAEs (B). Ranking plots indicate the probability of the highest to lowest risk of different adverse events.</p>

Supplementary Files

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