

Comparative efficacy and safety of PD-1/PD-L1 immunotherapies for non-small cell lung cancer: a network meta-analysis

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Abstract. – **OBJECTIVE:** PD-1/PD-L1 inhibitors are a relatively new class of immunotherapeutic drugs approved for advanced non-small-cell lung cancer. The purpose of this study was to conduct a network meta-analysis to compare the safety and efficacy of these immune checkpoint inhibitors (ICIs).

MATERIALS AND METHODS: We used Bayesian network meta-analysis methods to evaluate the efficacy and safety of the included treatments. We further analyzed subgroups based on PD-L1 expression level, histology type, and line of the treatment setting.

RESULTS: We identified 19 RCTs, including 12,753 patients. In the analysis of all-comers, the pembrolizumab/chemotherapy combination ranked best for overall survival (OS) and progression-free survival (PFS). Durvalumab was the only ICI treatment that showed no benefit over chemotherapy. In the first-line setting only, in terms of OS, atezolizumab, pembrolizumab/chemotherapy, and nivolumab/ipilimumab ranked as the best treatments for patients with PD-L1 expression levels of $\geq 50\%$, 1-49%, and $< 1\%$, respectively. Nivolumab, atezolizumab, pembrolizumab, and durvalumab all had lower odds of grade 3 or greater treatment-related adverse events (TRAEs) compared to chemotherapy. With the addition of chemotherapy to any ICI regimen, the odds of TRAEs increased in a considerable and statistically significant way.

CONCLUSIONS: While the pembrolizumab/chemotherapy combination was the most effective therapy in the overall cohort of all-comers, treatment preferences varied by treatment-line setting, tumor characteristics, and outcome of interest. In the first-line setting, the most effective treatments for patients with PD-L1 expressions of $\geq 50\%$, 1-49%, and $< 1\%$ were atezolizumab, pembrolizumab/chemotherapy, and nivolumab/ipilimumab, respectively.

Key Words:

Advanced non-small cell lung cancer (advanced NSCLC), Immune checkpoint inhibitors (ICIs), Pembrolizumab, Nivolumab, Atezolizumab, Durvalumab, Network meta-analysis (NMA).

Introduction

Lung cancer is the second most common cancer among both men and women in the United States. In 2013-2017, the rate of new cases of lung and bronchus cancer was 54.2 per 100,000 people per year, and the death rate was 40.2 per 100,000 people per year¹. The primary types of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). The latter is responsible for 80-85% of lung cancers, has squamous and non-squamous (NSCLC) histologic types, and is more commonly found in non-smokers, women, and younger adults². With the advent of modernized therapies, including immune checkpoint inhibitors, we have seen drastic improvements in 5-year relative survival rates³.

Immunotherapy, including immune checkpoint inhibitors, is a new type of treatment for lung cancer that has shown great potential^{4,5}. The Food and Drug Administration (FDA) has approved nivolumab, pembrolizumab, and atezolizumab for treating advanced NSCLC in 2015, 2015, and 2016, respectively⁶⁻⁸. Nivolumab and pembrolizumab are antibodies against programmed cell death protein1 (PD-1), and atezolizumab is an antibody against programmed death-ligand1 (PD-L1)⁶⁻⁸. Pembrolizumab is FDA approved to treat advanced NSCLC in people whose tumors lack an epidermal growth factor receptor (EGFR) mutation or an anaplastic lymphoma kinase (ALK) translocation and in whom at least half of their tumor cells express PD-L1^{9,10}. However, the pembrolizumab/chemotherapy combination has been approved to treat advanced non-squamous NSCLC regardless of PD-L1 expression¹¹. Atezolizumab has been approved to treat NSCLC patients with high ($\geq 50\%$) PD-L1 expression in patients who lack ALK or EGFR mutations¹².

Despite all these trials, deciding on an optimal regimen in practice is difficult when the trials are lacking in direct comparisons and have considerable variability, particularly in terms of the various PD-L1 expression profiles, histologic types, first *versus* second line therapies, monotherapies *versus* combination therapies, and endpoints measured. The aim of this study, therefore, was to conduct a network meta-analysis to assess both direct and indirect comparisons between various ICI regimens for efficacy and safety, to determine the optimal regimen for the all-comers overall cohort and specific advice for subgroups based on PD-L1 expression, histology, and line of treatment.

Materials and Methods

Search Strategy

This network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (flow chart diagram is shown in the [Supplementary Figure 1](#))¹³.

We systematically searched the PubMed and Embase databases for English-language articles published up to December 20, 2020 according to pre-selected keywords. Search terms and keywords included “non-small cell lung cancer”, “randomized,” “checkpoint inhibitor*”, “pembrolizumab”, “nivolumab”, “atezolizumab,” “durvalumab,” and “anti PD-1/anti PD-L1” ([Supplementary Table I](#)). The screening and selection processes were conducted independently by two coauthors (DW, LGS), with a third coauthor available to resolve disagreements (TQ).

Selection Criteria

The eligible studies should meet the following criteria: (I) studies based on phase III randomized controlled trials (RCTs); (II) studies enrolled patients with advanced non-small cell lung cancer; (III) studies reported OS and/or PFS as outcomes; (IV) studies where the experimental treatment arm was an FDA approved PD-1/PD-L1 inhibitors and the control arm was chemotherapy; (V) each arm had at least 100 patients; (VI) papers were written in English language. Studies failing to meet any of these criteria and studies sharing the same data set were excluded. However, if two articles were published pertaining to the same clinical trial, such as an update on overall survival after the initial publication, the most up-to-date data for each outcome was taken from each article.

Data Extraction

All study data were extracted in duplicate (DW, LGS) on a standardized form. Disagreements were resolved through consensus and consultation with a third examiner (JW or TQ) if necessary. We extracted the most updated overall survival (OS) and progression-free survival (PFS) as efficacy outcomes, and grade 3 or higher treatment-related adverse events (TRAEs) as safety outcomes. We extracted details of each treatment arm, patients treated in each arm, line of treatment assessed (first-line, or second-line or later), and tumor histology (squamous-cell, non-squamous cell, or mixed). We also extracted median follow-up time, the number of patients in each PD-L1 expression subgroup (PD-L1 $\geq 50\%$, 1-49%, or $<1\%$), and basic patient characteristics (median age and percentage of male, current or former smoker, and percent with non-squamous cell lung cancer). If any data were missing from the included articles, we searched ClinicalTrials.gov to fill in any gaps.

Quality Assessment

Two reviewers (LS and DW) assessed the potential risks of bias of included studies independently, using the Cochrane Collaboration’s Risk of Bias tool¹⁴, performed in RevMan statistical software (RevMan version 5.3). If required, a third reviewer (KY or SW) was invited to resolve any disagreements.

Statistical Analysis

We conducted a network meta-analysis (NMA) in the Bayesian framework to assess direct and indirect evidence, using “JAGS” and “GeMTC” packages in R software version 3.6.3^{15,16}. A Markov Chain Monte Carlo (MCMC) simulation based on the Bayesian method was performed with 10,000 adaptations and 100,000 iterations of each of the four Markov chains (automatically generated by “JAGS” sampler). One reviewer (DW) performed all statistical analyses, while interpretation was done by three reviewers (DW, LGS, FS).

The endpoints of interest of this NMA were OS and PFS, which were expressed as Hazard Ratios (HR) with their 95% credible intervals (CrIs), and safety outcomes were expressed as Odds Ratios (OR). To rank the therapies in order from best-to-worst, we carried out the ranking probability command and create league tables. In addition to analyses of all-comers (our overall cohort), we also conducted additional cohort analyses based on PD-L1 expression (high, $\geq 50\%$;

intermediate, 1-49%; and low, <1%), histological type, and treatment-line to provide more practical evidence for clinical use and to reduce the heterogeneity between studies. Statistical significance was defined at a two-side α level of less than 0.05.

Sensitivity Analysis

To determine the consistency of our model, we created both fixed and random models and compared the results for each analysis cohort. If the difference of DICs of each model was less than 5 (DIC is an estimate of expected predictive error), we considered the analysis to be consistent¹⁷.

Heterogeneity Analysis

Heterogeneity was calculated using the within-study Q statistic^{18,19}, between-study variance τ^2 , and heterogeneity statistic I^2 . We conducted the `anote` command to perform the analysis of heterogeneity to yield an I-square (I^2) value. We interpreted I^2 values of 25%, 50%, and 75% as low, moderate, and high heterogeneity, respectively¹⁸. If $I^2 < 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used²⁰.

Results

Studies Included in the NMA

A total of 1,827 articles were identified from the initial database search, 345 from PubMed and 1,482 from Embase. After removing 346 duplicate records, 1,481 articles were screened. The initial search results and selection process are showed in [Supplementary Figure 1](#). Finally, 31 articles describing 19 RCTs that involved 12,753 patients and 9 treatment regimens were included in this NMA. Details of trials are showed in Table I.

Characteristics of Studies

Experimental arms in 12 trials studied consisted of ICI monotherapies (KN-010^{21,22}, KN-024²³⁻²⁵, KN-033²⁶, KN-042^{27,28}, CM 017²⁹⁻³¹, CM 026³², CM 057³³, CM 078³⁴, CM 227 [Part 1]³⁵⁻³⁷, OAK^{38,39}, IMpower110⁴⁰, MYSTIC⁴¹, and ARCTIC [Study B]⁴²). Experimental arms in 7 trials studied ICIs in combination with chemotherapy (KN-189^{43,44}, KN-407⁴⁵⁻⁴⁷, CM 227 [Part 1], CM 227 [Part 2]⁴⁸, IMpower130⁴⁹, IMpower 131⁵⁰, IMpower132⁵¹). Additionally, one trial evaluated a combination of an anti-PD-1 antibody with a CTLA-4 antibody (Nivolumab/Ipilimumab; CM Part 1^{52,53}). The network plot of eligible comparisons is shown in Figure 1.

Assessment of Included Trials

The risk of bias assessment of included trials is presented in [Supplementary Figure 2](#). Overall, 18 trials were considered to have low risk of bias for the overall survival outcome. One trial (CM 227 Part 2) was considered to have an unclear risk of bias as three domains were assessed as having an unclear risk. Most methodological information was confirmed by accessing trial protocols (unable to find protocols for CM 227 Part 2 and OAK). In the selection bias domain, 18 trials were considered low risk, and one (CM 227 Part 2) was considered unclear risk. In the reporting bias domain, 18 trials were considered low risk, and one (CM 227 Part 2) was considered unclear risk. In the performance bias domain, all trials were considered to be low risk for the overall survival outcome as this is unlikely to be affected by the lack of blinding in the open trial design. Only two trials (KN-189 and KN-407) had a low risk of bias for PFS, as these were the only double-blind trials (bias assessments for PFS not shown in [Supplementary Figure 2](#)). In the detection bias domain, all trials were considered low risk for the overall survival outcome as this is unlikely to be affected by lack of blinding. Ten trials (KN-010, KN-024, KN-033, KN-042, KN-189, KN-407, CM 017, CM 026, CM 227 Part 1, MYSTIC) were also considered low risk for the PFS outcome, as they used blinded independent central reviewers for radiographic assessment of progression (bias assessments for PFS not shown in [Supplementary Figure 2](#)). All trials were considered low risk for attrition bias. Most trials allowed crossover, and this was considered to be a source of other potential bias.

Cohort Description

Twelve trials were in first-line settings and 7 trials were in second-line or later settings (the ARCTIC trial was in the third-line or later setting, but we grouped it in with the second-line or later trials in our analysis). Only 3 trials were specifically targeted at patients with squamous cell carcinomas (CM 017, IMpower131, and KN-407), 4 trials were targeted at patients with non-squamous cell carcinomas, and 12 included NSCLC patients with both histology types. The majority of patients were male and were either current or former smokers.

While most studies directly grouped participants by PD-L1 Tumor Proportion Score (TPS), some immunohistochemistry diagnostic assays measured PD-L1 expression on both tumor cells (TC) and tumor-infiltrating immune cells (IC).

Table I. Details of all included trials.

Study	Study characteristics					D-L1 expression			Patient characteristics			
	Treatment details	Sample size	Line of treatment	Histology types	Median follow-up (months)	≥50% (n)	1%-49% (n)	<1% (n)	% Male	% of current or former smokers	% of non-squamous	Median age
KEYNOTE -010	Pem	690	Second or late	Mixed	42.6	290	400	0	62%	82%	70%	63
	Chemo	343				152	191	0	61%	78%	70%	62
KEYNOTE -024	Pem	154	First-line	Mixed	25.2	154	0	0	59.7%	96.8%	81.2%	64.5
	Chemo	151				151	0	0	62.9%	87.4%	82.1%	66
KEYNOTE -033	Pem	213	Second or later	Mixed	18.8	114	112	0	73.7%	N/A	N/A	60.6†
	Chemo	212				98	98	0	77.4%	N/A	N/A	61.0†
KEYNOTE -042	Pem	637	First-line	Mixed	14	299	338	0	71%	78%	62%	63
	Chemo	637				300	337	0	71%	78%	61%	63
KEYNOTE -189	Pem+Chemo	410	First-line	Non-SCC	23.1	132	128	127	62.0%	88.3%	100%	65
	Chemo	206				70	58	63	52.9%	87.9%	100%	63.5
KEYNOTE -407	Pem+Chemo	278	First-line	SCC	14.3	73	103	95	79.1%	92.1%	0%	65
	Chemo	281				73	104	99	83.6%	93.2%	0%	65
CheckMate 017	Niv	135	Second or later	SCC	36.6 (minimum)	17	NA	54	82%	90%	0%	63
	Chemo	137				12	NA	52	71%	94%	0%	63
CheckMate 026	Niv	271	First-line	Mixed	13.5	88	NA	0	89%	88%	76%	63
	Chemo	270				126	NA	0	88%	87%	76%	65
CheckMate 057	Niv	292	Second or later	Non-SCC	36.6 (minimum)	66	NA	108	53%	79%	100%	61
	Chemo	290				46	NA	101	58%	78%	64	
CheckMate 078	Niv	338	Second or late	Mixed	25.9 (minimum)	NA	NA	138	78%	70%	61%	60
	Chemo	166				NA	NA	67	81%	71%	60%	60

Continued

Table 1 (Continued). Details of all included trials.

Study	Study characteristics					D-L1 expression			Patient characteristics			
	Treatment details	Sample size	Line of treatment	Histology types	Median follow-up (months)	≥50% (n)	1%-49% (n)	<1% (n)	% Male	% of current or former smokers	% of non-squamous	Median age
CheckMate 227 (Part 1)	Niv+Ipi	583	First-line	Mixed	29.3 (minimum)	205	191	187	67.4%	85.2%	71.9%	64
	Niv	396				214	182	0	68.7%	86.4%	70.5%	64
	Niv+Chemo	177				0	1	176	73.4%	83.1%	75.7%	64
	Chemo	583				192	205	186	66.0%	85.6%	72.2%	64
CheckMate 277 (Part 2)	Niv+Chemo	377	First-line	Mixed	19.5 (minimum)	NA	NA	NA	NA	NA	NA	NA
	Chemo	378				NA	NA	NA	NA	NA	NA	NA
OAK	Ate	425	Second or later	Mixed	26 (minimum)	72	173	180	61%	80%	74%	63
	Chemo	425				65	161	199	61%	83%	74%	64
IMpower110	Ate	277	First-line	Mixed	13.4	107	170	0	70.8%	86.6%	69.3%	64
	Chemo	277				98	179	0	69.7%	87.4%	69.7%	65
IMpower130	Ate+Chemo	451	First-line	Non-SCC	18.5	88	128	235	59%	89%	100%	64
	Chemo	228				42	65	121	59%	92%	100%	65
IMpower131	Ate+Chemo	343	First-line	SCC	26.8	48	134	161	80%	77.20%	0%	65
	Chemo	340				44	126	170	80%	77.20%	0%	63
IMpower132	Ate+Chemo	292	First-line	Non-SCC	28.4	25	63	88	66.4%	87%	100%	64
	Chemo	286				20	72	75	66.4%	90%	100%	63
MYSTIC	Dur	374	First-Line	Mixed	30.2	118	161	95	68.4%	84.8%	71.4%	65
	Chemo	372				107	182	83	67.2%	86.0%	71.5%	64
ARCTIC (Study B)	Dur	117	Third-line or later	Mixed	9.1	0	N/A	52	62.4%	76.1%	75.2%	63
	Chemo	118				0	N/A	58	68.6%	81.4%	76.3%	65

Abbreviations: NA: not available; Ate: atezolizumab; Pem: pembrolizumab; Ipi: ipilimumab; Niv: nivolumab; Dur: durvalumab; Chemo: chemotherapy; SCC: Squamous Cell Carcinoma. Notes: † Mean age

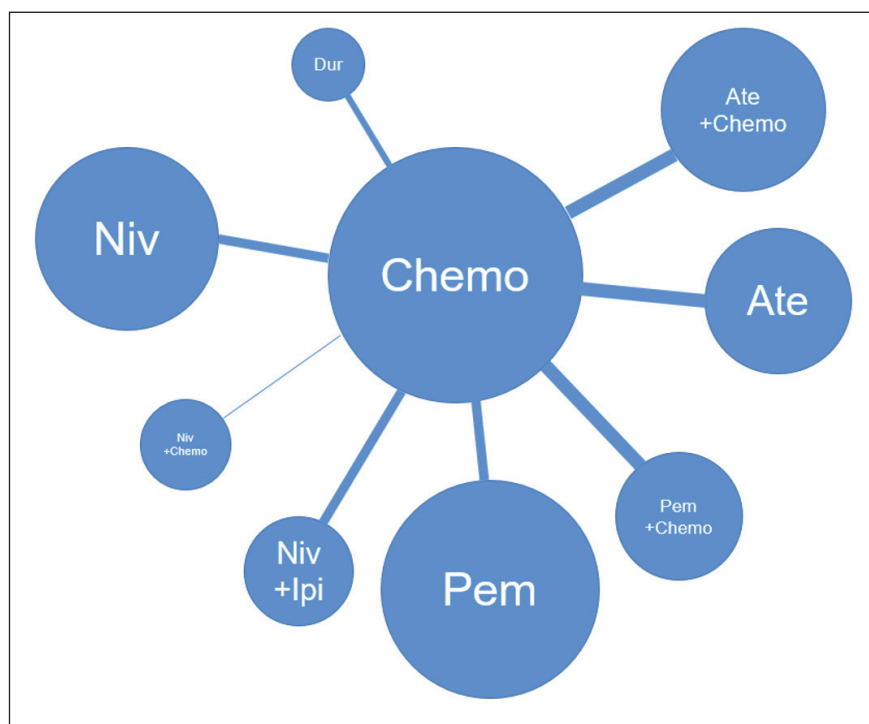


Figure 1. Network of eligible comparisons. The size of the nodes is proportional to the number of patients randomized to receive the treatment. The width of the lines is proportional to the number of trials comparing the connected treatments. Abbreviations: Pem, pembrolizumab; Ate, atezolizumab; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Chemo, chemotherapy.

To group the patients according to PD-L1 expression level uniformly, “TPS \geq 50%” and “TC3 or IC3” were analyzed as PD-L1 \geq 50%; “TPS<1%” and “TC0 or IC0” as PD-L1<1%; and “1 \leq TPS \leq 49%” and “TC1,2 or IC1,2” as 1% \leq PD-L1 \leq 49%.

Overall Survival in All-Comers Cohort

The NMA model for OS in the all-comers cohort, 19 of 19 studies reported OS in all-comers. This analysis compared 8 experimental treatments, with 7,053 patients, to a chemotherapy control arm with 5,700 patients (see Table II). Results based on the OS-NMA estimates (Figure 2) between each of the experimental arms showed that pembrolizumab/chemotherapy (HR=0.63; 95%CrI, 0.55-0.74) had a 37% lower risk of death versus chemotherapy, performing favorably compared to the other experimental treatments. Pembrolizumab/chemotherapy had the highest probability (87%) of ranking as the best treatment (Supplementary Table II). Nivolumab/ipilimumab had the highest probability (38%) of ranking as the second best treatment, with a 27% lower risk of death versus chemotherapy (HR=0.73, 95%CrI, 0.64-0.84). Pembrolizumab (HR=0.74; 95%CrI, 0.68-0.81), atezolizumab (HR=0.77; 95%CrI, 0.67-0.89), nivolumab (HR=0.81; 95%CrI, 0.75-0.89), nivolumab/chemotherapy

(HR=0.81; 95%CrI, 0.68-0.97), and atezolizumab/chemotherapy (HR=0.85; 95%CrI, 0.76-0.95) all performed better than chemotherapy. Durvalumab was the only ICI regimen that did not have a statistically significant benefit over chemotherapy (HR=0.92, 95%CrI, 0.79-1.10).

In the indirect analysis, pembrolizumab/chemotherapy performed better than atezolizumab/chemotherapy, nivolumab monotherapy, and durvalumab. Durvalumab was inferior to nivolumab/chemotherapy, pembrolizumab, and pembrolizumab/chemotherapy. No other significant differences were observed between treatments. All the comparisons are shown in Figure 2.

Progression-Free Survival in All-Comers Cohort

In the NMA for PFS in the all-comers cohort, 18 of 19 studies reported PFS of overall patients. This analysis compared 8 experimental treatments, with 6,856 patients, to the control arm with 5,328 patients. In the direct comparisons, all PD-1/PD-L1 immune checkpoint inhibitor regimens in the experimental arms, except nivolumab and durvalumab, evidenced significantly greater PFS benefit than chemotherapy (Supplementary Figure 3A). Compared with chemotherapy, pembrolizumab/chemotherapy (HR=0.52; 95% CrI, 0.46-0.60) had the greatest benefits in PFS.

Table II. Extracted outcome data from all included trials.

Study	Treatment details	Line of treatment	OS-HR (95%CrI)				PFS-HR(95%CrI)				Grade ≥ TRAEs %
			Overall	PD-L1 ≥50%	PD-L1 1%-49%	PD-L1 <1%	Overall	PD-L1 ≥50%	PD-L1 1%-49%	PD-L1 <1%	
KN-010	Pem Chemo	Second or later	0.69 (0.60-0.80)	0.53 (0.42-0.66)	0.78 (0.65-0.94)	NA	0.83 (0.72-0.96)	0.57 (0.45-0.71)	1.02 (0.85-1.24)	NA	16.1% 36.6%
KN-024	Pem Chemo	First-line	0.62 (0.48-0.81)	0.62 (0.48-0.81)	NA	NA	0.50 (0.37-0.68)	0.50 (0.37-0.68)	NA	NA	31.2% 53.3%
KN-033	Pem Chemo	Second or later	0.75 (0.60-0.95)	0.83 (0.61-1.14)	N/A	N/A	0.84 (0.66-1.08)	0.76 (0.54-1.07)	N/A	N/A	11% 47%
KN-042	Pem Chemo	First-line	0.82 (0.71-0.93)	0.70 (0.58-0.86)	0.91 (0.77-1.09)	NA	1.05 (0.93-1.19)	0.83 (0.69-1.00)	1.27 (1.08-1.50)	NA	18% 41%
KN-189	Pem+Chemo Chemo	First-line	0.56 (0.45-0.70)	0.59 (0.39-0.88)	0.62 (0.42-0.92)	0.52 (0.36-0.74)	0.48 (0.40-0.58)	0.36 (0.26-0.51)	0.51 (0.36-0.73)	0.64 (0.47-0.89)	71.9%† 66.8%†
KN-407	Pem+Chemo Chemo	First-line	0.71 (0.58-0.88)	0.79 (0.52-1.21)	0.59 (0.42-0.84)	0.79 (0.56-1.11)	0.57 (0.47-0.69)	0.43 (0.29-0.63)	0.52 (0.38-0.71)	0.67 (0.49-0.91)	56.5% 55.7%
CM 017	Niv Chemo	Second or later	0.62 (0.48-0.80)	0.68 (0.27-1.66)	NA	0.60 (0.40-0.90)	0.63 (0.48-0.83)	NA	NA	0.66 (0.44-1.01)	6.9% 57.4%
CM 026	Niv Chemo	First-line	1.08 (0.87-1.34)	0.90 (0.63-1.29)	NA	NA	1.19 (0.97-1.46)	1.07 (0.77-1.49)	NA	NA	18.4% 51.7%
CM 057	Niv Chemo	Second or later	0.74 (0.62-0.89)	0.35 (0.22-0.55)	NA	0.91 (0.68-1.21)	0.89 (0.75-1.07)	NA	NA	1.19 (0.88-1.61)	10.5% 53.7%
CM 078	Niv Chemo	Second or later	0.75 (0.61-0.93)	NA	NA	0.73 (0.53-1.02)	0.79 (0.65-0.98)	NA	NA	0.77 (0.56-1.07)	13.4% 49.4%
CM 227 (Part 1)	Niv+Ipi Chemo	First-line	0.73 (0.64-0.84)	0.70 (0.55-0.90)	NA	0.62 (0.48-0.78)	0.79 (0.69-0.91)	0.62 (0.49-0.79)	NA	0.75 (0.59-0.96)	34.2% 37.0%
	Niv Chemo	First-line	0.88 (0.75-1.04)	NA	NA	NA	0.99 (0.84-1.17)	NA	NA	NA	19.9% 37.0%
	Niv+Chemo Chemo	First-line	NA	NA	NA	0.78 (0.62-0.98)	0.74 (0.58-0.94)	NA	NA	0.73 (0.56-0.95)	58.1% 37.0%
CM 277 (Part 2)	Niv+Chemo Chemo	First-line	0.81 (0.67-0.97)	NA	NA	NA	0.62 (0.52-0.73)	NA	NA	NA	NA NA
OAK	Ate Chemo	Second or later	0.75 (0.64-0.89)	0.40 (0.27-0.61)	NA	0.77 (0.61-0.97)	0.93 (0.80-1.08)	0.62 (0.43-0.89)	NA	1.00 (0.80-1.24)	14.9% 42.6%
IMpower 110	Ate Chemo	First-line	0.83 (0.65-1.07)	0.59 (0.40-0.89)	1.04 (0.76-1.44)	NA	0.77 (0.63-0.94)	0.63 (0.45-0.88)	0.90 (0.71-1.15)	NA	12.9% 44.5%
IMpower 130	Ate+Chemo Chemo	First-line	0.79 (0.64-0.98)	0.84 (0.51-1.39)	0.70 (0.45-1.08)	0.81 (0.61-1.08)	0.64 (0.54-0.77)	0.51 (0.34-0.77)	0.61 (0.43-0.85)	0.72 (0.56-0.91)	74.8% 60.7%
IMpower 131	Ate+Chemo Chemo	First-line	0.88 (0.73-1.05)	0.48 (0.29-0.81)	1.08 (0.81-1.45)	0.87 (0.67- 1.13)	0.71 (0.60-0.85)	0.41 (0.25-0.68)	0.70 (0.54-0.91)	0.82 (0.65-1.04)	69.2% 58.4%
IMpower 132	Ate+Chemo Chemo	First-line	0.86 (0.71-1.06)	0.73 (0.31-1.73)	1.18 (0.80-1.76)	0.67 (0.46-0.96)	0.60 (0.49-0.72)	0.46 (0.22-0.96)	0.80 (0.55-1.16)	0.45 (0.31-0.64)	58.4% 43.1%
MYSTIC	Dur Chemo	First-Line	0.96 (0.81-1.13)	0.76 (0.55-1.04)	NA	1.18 (0.86-1.62)	NA	NA	NA	NA	14.9% 33.8%
ARCTIC (Study B)	Dur Chemo	Third-line or later	0.80 (0.59-1.08)	NA	NA	0.80 (0.53-1.22)	0.87 (0.65-1.16)	NA	NA	0.76 (0.51-1.15)	12.8% 36.4%

Abbreviations: KN: KEYNOTE; CM: CheckMate; NA: not available; TRAEs: Treatment-Related Adverse Events; Ate: atezolizumab; Pem: pembrolizumab; Ipi: ipilimumab; Niv: nivolumab; Dur: durvalumab; Chemo: chemotherapy. Notes: †Treatment-related adverse events were not available, so data on all Grade ≥3 adverse events was used

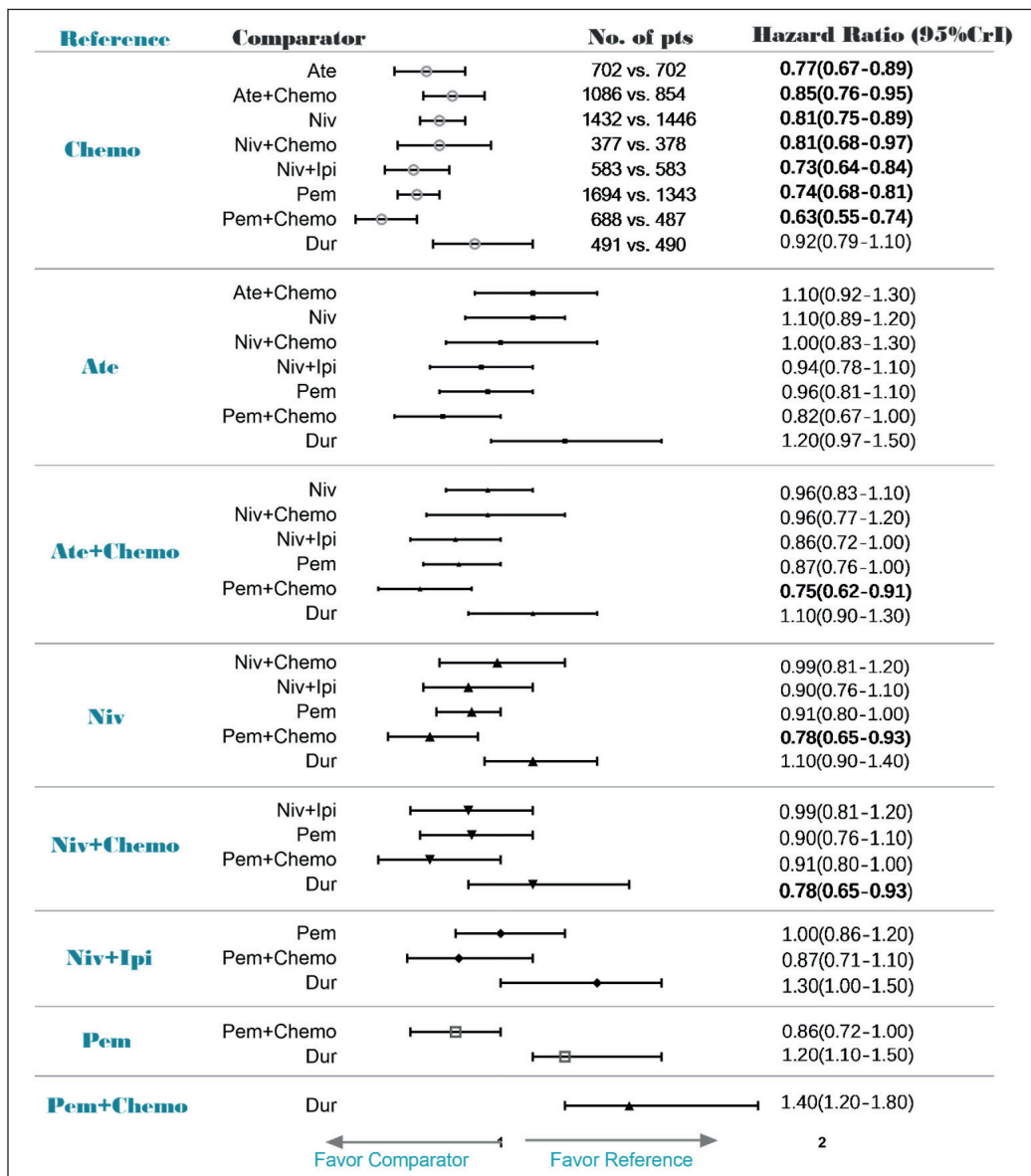


Figure 2. Network Meta-Analysis of Overall Survival (OS-NMA) in the all-comers cohort. Abbreviations: Pem, pembrolizumab; Ate, atezolizumab; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Chemo, chemotherapy.

Results from the indirect comparisons NMA found that pembrolizumab/chemotherapy was estimated to be consistently better than all the other ICI treatments evaluated: atezolizumab (HR=0.60; 95%CrI, 0.50-0.72), atezolizumab/chemotherapy (HR=0.80; 95%CrI, 0.68-0.95), nivolumab (HR=0.57, 95%CrI, 0.49-0.67), nivolumab/chemotherapy (HR=0.79; 95%CrI, 0.65-0.96), and nivolumab/ipilimumab (HR=0.66; 95%CrI, 0.55-0.80; **Supplementary Figure 3A**). Further, when compared to pembrolizumab/chemotherapy, durvalumab had worse PFS outcomes (HR=1.70; 95%CrI, 1.20-2.30; **Supplementary Figure 3A**).

Treatment-Related Adverse Events (Grade-3 or Greater) in the All-Comers Cohort

Table II summarizes the incidence of grade-3 or greater treatment-related adverse events (TRAEs) in each trial. Compared to chemotherapy, the odds of grade-3 or greater treatment-related adverse events were lower for nivolumab (OR=0.15; 95%CrI, 0.09-0.26), atezolizumab (OR=0.21; 95%CrI, 0.09-0.47), pembrolizumab (OR=0.28; 95%CI, 0.15-0.49), and durvalumab (OR=0.30; 95%CrI, 0.13-0.67) monotherapies (Figure 3). These comparisons included 2,878, 1,404, 3,037, and 981 patients, respectively. The risk

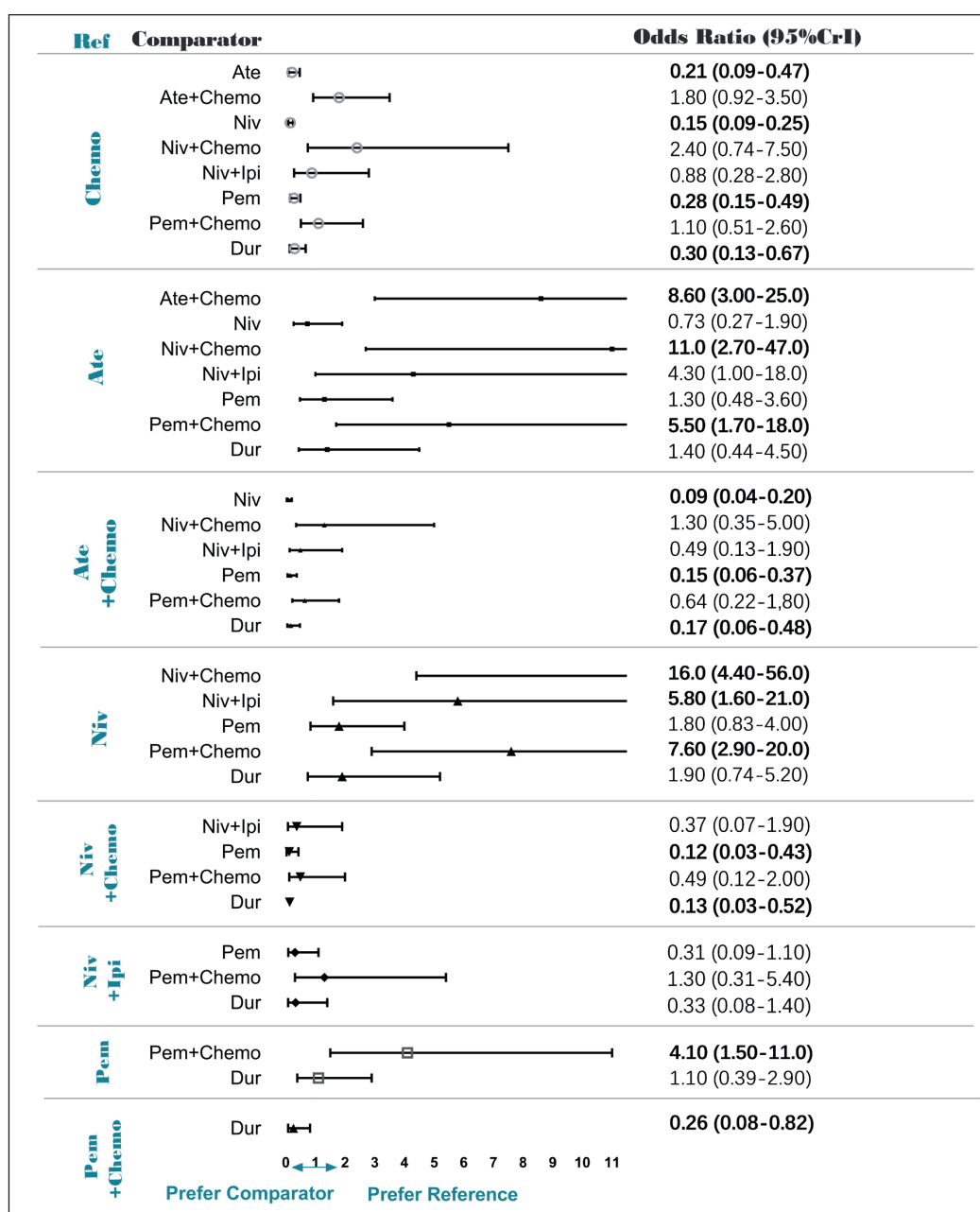


Figure 3. Network Meta-Analysis of the odds of grade 3 or greater treatment-related adverse events compared with chemotherapy in the all-comers cohort. Abbreviations: Pem, pembrolizumab; Ate, atezolizumab; Dur, durvalumab; Ipi, ipilimumab; Niv, nivolumab; Chemo, chemotherapy.

of grade-3 or greater TRAEs increased significantly with combination regimens (Figure 3): pembrolizumab/chemotherapy (OR=4.10; 95%CrI, 1.50-11.0, when compared to pembrolizumab), nivolumab/ipilimumab (OR=5.80; 95%CrI, 1.60-21.0, when compared to nivolumab), nivolumab/chemotherapy (OR=16.0; 95%CrI, 4.40-56.0, when compared to nivolumab), or atezolizumab/chemotherapy (OR=8.60; 95%CrI, 3.00-25.0, when compared to atezolizumab).

NMA by PD-L1 Expression Cohorts

PD-L1 ≥50% cohort

The OS-NMA for the PD-L1 ≥50% cohort was based on 18 trials evaluating 7 experimental treatment regimens with 1,896 patients, and 1,596 in the chemotherapy control arm. Results from the NMA show that all ICI regimens, except durvalumab, were significantly better than

chemotherapy in terms of OS (**Supplementary Figure 4A**). Atezolizumab yielded the greatest benefit in OS over chemotherapy (HR=0.49; 95%CrI, 0.37-0.65) with the highest probability of ranking the best (79%; **Supplementary Table III**). When we explored indirect comparisons, no other significant differences were found between ICI regimens.

The PFS-NMA for the PD-L1 $\geq 50\%$ cohort was based on 13 trials evaluating 6 experimental treatment regimens with 1,695 patients in the experimental arms, and 1,431 patients in the control arms. Results from direct comparisons between experimental arms and control arms show that all ICI treatments, except nivolumab, had significantly better PFS outcomes than chemotherapy (**Supplementary Figure 3B**). When compared directly to chemotherapy, pembrolizumab/chemotherapy had the greatest PFS benefit (HR=0.39; 95%CrI, 0.30-0.50). Based on indirect comparisons, pembrolizumab/chemotherapy also had significant PFS benefits compared to all other treatments (**Supplementary Figure 3B**). While nivolumab/ipilimumab was still inferior to pembrolizumab/chemotherapy, it did show a statistically significant benefit over nivolumab monotherapy (HR=0.58; 95%CrI, 0.39-0.87).

PD-L1 1%-49% cohort

The OS-NMA for the PD-L1 1%-49% cohort is based on 8 trials and 4 experimental treatments in 1,464 patients, and 1,132 patients in the non-ICI control arms. Results from direct comparisons showed that, of the 4 ICI treatments, only pembrolizumab/chemotherapy (HR=0.60; 95%CrI, 0.46-0.79) and pembrolizumab monotherapy (HR=0.85; 95%CrI, 0.75-0.96) performed better than chemotherapy. Neither atezolizumab monotherapy nor atezolizumab/chemotherapy had any statistically significant difference in survival compared to chemotherapy (**Supplementary Figure 4B**). Indirect estimates showed that pembrolizumab/chemotherapy had improved overall survival compared to pembrolizumab (HR=0.71; 95%CrI, 0.53-0.95), atezolizumab/chemotherapy (HR=0.60; 95%CrI, 0.43-0.84), and atezolizumab monotherapy (HR=0.58; 95%CrI, 0.38-0.88). Pembrolizumab/chemotherapy had a 98% probability of ranking as the best treatment (**Supplementary Table IV**).

The PFS-NMA for the PD-L1 1%-49% cohort is based on 8 trials evaluating 4 experimental treatments with 1,464 patients in the experimental arm, with 1,123 patients in the control arms. Results

from direct comparisons shows pembrolizumab/chemotherapy (HR=0.52; 95%CrI, 0.41-0.65) and atezolizumab/chemotherapy (HR, 0.70; 95%CrI, 0.58-0.83) both had statistically better PFS outcomes compared chemotherapy (**Supplementary Figure 3C**). Pembrolizumab monotherapy (HR=1.20; 95%CrI, 1.00-1.30) and atezolizumab monotherapy (HR=0.90; 95%CrI, 0.71-1.10) had no statistically significant benefits over chemotherapy. Based on the indirect estimates, pembrolizumab/chemotherapy displayed statistically significant PFS benefits over atezolizumab and pembrolizumab, but not over atezolizumab/chemotherapy (**Supplementary Figure 3C**).

PD-L1 <1% cohort

The OS-NMA for the PD-L1 <1% cohort is based on 12 trials evaluating 7 experimental treatments in 1,696 patients, with 1,274 patients in the non-ICI control arms (**Supplementary Figure 4C**). According to the results of direct comparisons, all of the experimental ICI treatments, except durvalumab, evidenced better OS outcomes than chemotherapy. Based on indirect comparisons NMA, the only statistically significant differences between ICI treatments were observed for durvalumab, which had a higher risk of death compared to pembrolizumab (HR=1.70; 95%CrI, 1.20-2.40) and pembrolizumab/chemotherapy (HR=1.60; 95%CrI, 1.10-2.20; **Supplementary Figure 4C**). Nivolumab/ipilimumab had the highest probability of ranking as the best treatment (54%) with a 38% reduction in risk of death compared to chemotherapy (HR=0.62; 95%CrI, 0.49-0.79), while pembrolizumab/chemotherapy had the highest probability of ranking as the second-best treatment (37%) with a 35% reduction in risk of death compared to chemotherapy (HR=0.65; 95%CrI, 0.51-0.83; **Supplementary Figure 4C** and **Supplementary Table V**).

The PFS-NMA for the PD-L1 <1% cohort is based on 11 trials evaluating 7 experimental treatments in 1,601 patients, with 1,191 patients in the non-ICI control arms (**Supplementary Figure 3D**). According to the direct comparisons, pembrolizumab/chemotherapy (HR=0.66; 95%CrI, 0.52-0.82), atezolizumab/chemotherapy (HR=0.70; 95%CrI, 0.60-0.82), nivolumab/chemotherapy (HR=0.73; 95%CrI, 0.56-0.95), and nivolumab/ipilimumab (HR=0.75; 95%CrI, 0.59-0.96) showed statistically significant PFS benefits over chemotherapy. None of the monotherapies (atezolizumab, nivolumab, or durvalumab) had any statistically significant differences in out-

comes compared to chemotherapy. According to the analysis of indirect comparisons, there were no statistically significant differences between any of the combination therapies (**Supplementary Figure 3D**).

Subgroup Analysis Based on Histology Type and Treatment Line Setting

NMA by histology type

Information of histology type is reported in all 19 trials: 12 trials had mixed histology types, 4 had only non-squamous NSCLC patients, and 3 had only squamous NSCLC patients.

The subgroup of non-squamous NSCLC patients included 4 trials evaluating 3 experimental treatments in 1,445 patients, with 1,010 patients in the non-ICI control arms (Table I). In the analysis of direct comparisons for OS in non-squamous NSCLC patients (**Supplementary Figure 5A**), all the experimental treatments show greater OS compared to chemotherapy. Compared to chemotherapy, pembrolizumab/chemotherapy had the greatest OS benefit (HR=0.56; 95%CrI, 0.45-0.70), followed by nivolumab monotherapy (HR=0.74; 95%CrI, 0.62-0.89), and atezolizumab/chemotherapy (HR=0.83; 95%CrI, 0.71-0.96). In the indirect comparisons analysis, pembrolizumab/chemotherapy displayed greater OS benefits over atezolizumab/chemotherapy (HR=0.68; 95%CrI, 0.52-0.88), but no other significant differences were found between the ICI treatments. In the analysis of direct comparisons for PFS in non-squamous NSCLC patients (**Supplementary Figure 5C**), when compared to chemotherapy, the greatest benefit in progression-free survival was seen with pembrolizumab/chemotherapy (HR=0.48; 95%CrI, 0.40-0.58), followed by atezolizumab/chemotherapy (HR=0.62; 95%CrI, 0.55-0.71). No significant benefit over chemotherapy was seen with nivolumab monotherapy (HR=0.89; 95%CrI, 0.74-1.10). In the indirect comparisons analysis, nivolumab displayed worse PFS outcomes compared to other regimens.

The subgroup of squamous NSCLC patients included 3 trials evaluating 3 ICI treatments in 756 patients, with 758 patients in the chemotherapy control arm (Table I). Direct comparisons demonstrated pembrolizumab/chemotherapy (HR=0.71; 95%CrI, 0.58-0.87) and nivolumab (HR=0.62; 95%CrI, 0.48-0.80) performed better than chemotherapy in terms of OS, but atezolizumab/chemotherapy did not (**Supplementary Figure 4B**). No significant difference was observed in

OS between nivolumab and pembrolizumab/chemotherapy. Based on the direct comparisons for PFS, nivolumab (HR=0.63; 95%CrI, 0.48-0.83), pembrolizumab/chemotherapy (HR=0.57; 95%CrI, 0.47-0.69), and atezolizumab/chemotherapy (HR=0.71; 95%CrI, 0.60-0.85) all displayed PFS benefits in comparison to chemotherapy (**Supplementary Figure 5D**). However, based on the indirect comparisons analysis, there were no significant differences among them (**Supplementary Figure 5D**).

NMA by treatment line setting

Of the 19 included trials, 12 investigated ICIs in the first-line setting and 7 were in the setting of second-line or later (one of which was only in the third-line or later setting).

In the first-line setting subgroup, the 12 trials investigated 8 ICI treatment regimens in 6,620 patients, with 4,009 patients in the non-ICI control arms. In the OS analysis of the all-comers cohort in the first-line setting (**Supplementary Figure 6A**), five regimens showed statistically significant benefits over chemotherapy: pembrolizumab/chemotherapy (HR=0.64; 95%CrI, 0.55-0.74), nivolumab/ipilimumab (HR=0.73; 95%CrI, 0.64-0.84), pembrolizumab (HR=0.77; 95%CrI, 0.69-0.87), nivolumab/chemotherapy (HR=0.81; 95%CrI, 0.67-0.98), and atezolizumab/chemotherapy (HR=0.85; 95%CrI, 0.76-0.95). Atezolizumab, nivolumab, and durvalumab showed no statistically significant benefit over chemotherapy. Among the regimens which showed benefit over chemotherapy, the indirect comparisons analysis showed that pembrolizumab/chemotherapy had statistically significant OS benefits over atezolizumab/chemotherapy (HR=0.75; 95%CrI, 0.62-0.91; **Supplementary Figure 6A**). However, there were no significant differences when compared to pembrolizumab, nivolumab/ipilimumab, nivolumab/chemotherapy, or atezolizumab/chemotherapy (**Supplementary Figure 6A**). Pembrolizumab/chemotherapy had the highest probability (86%) of ranking as the best treatment for all-comers in the first-line setting subgroup (**Supplementary Table VI**).

When stratifying the analysis for treatments in the first-line setting by PD-L1 expression, the findings differed. For the PD-L1 \geq 50% cohort in the first-line setting (**Supplementary Figure 6B**), all the experimental treatments except nivolumab and durvalumab had statistically significant OS benefits over chemotherapy. While there were no significant OS differences between the experimen-

tal treatments, atezolizumab (HR=0.59; 95%CrI, 0.40-0.88, when compared to chemotherapy) was the most favorable treatment with a 47% of probability of ranking the best (**Supplementary Table VII**). For the PD-L1 1-49% cohort in the first-line setting (**Supplementary Figure 6C**), only pembrolizumab/chemotherapy (HR=0.60; 95%CrI, 0.46-0.78) showed significant OS benefits over chemotherapy and had the highest probability (99%) of ranking as the best treatment (**Supplementary Table VIII**). For the PD-L1<1% cohort in the first-line setting (**Supplementary Figure 6D**), nivolumab/ipilimumab (HR=0.62; 95%CrI, 0.49-0.79), pembrolizumab/chemotherapy (HR=0.65; 95%CrI, 0.51-0.83), nivolumab/chemotherapy (HR=0.80; 95%CrI, 0.68-0.95), and atezolizumab/chemotherapy (HR=0.80; 95%CI, 0.68-0.95) all had statistically significant OS benefits over chemotherapy, but durvalumab did not. Among the regimens which performed better than chemotherapy in the direct analysis, there were no statistically significant differences when comparing them in the indirect analysis. Nivolumab/ipilimumab had the highest probability (57%) of ranking as the best treatment, while pembrolizumab/chemotherapy had the highest probability (45%) of ranking as the second best (**Supplementary Table IX**).

In the second-line or later subgroup, the 7 trials investigated 4 ICI treatment regimens in 2,208 patients, with 1,691 patients in the chemotherapy control arms. In terms of OS of all-comers in the second-line or later treatment setting subgroup, pembrolizumab (HR=0.71; 95%CrI, 0.63-0.80), nivolumab (HR=0.71; 95%CrI, 0.63-0.81), and atezolizumab (HR=0.75; 95%CrI, 0.64-0.88) all showed statistically significant OS benefits when compared to chemotherapy (**Supplementary Figure 6E**). However, durvalumab (HR=0.80; 95%CrI, 0.59-1.10) did not (**Supplementary Figure 6E**). The indirect comparisons analysis found no statistically significant differences between any other treatments. Pembrolizumab and nivolumab had similar OS benefits and similar ranking probabilities as the best treatment (38% and 31%, respectively), so either could be considered the best treatment choice for second-line or later therapies (**Supplementary Table X**).

Discussion

This novel NMA assessed the comparative efficacy and safety of anti-PD-L1/anti-PD-1 immune checkpoint inhibitor (ICI) treatments for

advanced NSCLC patients, with numerous subgroup analyses. In our NMA, all ICI treatment regimens, except durvalumab, showed promising overall survival benefits over chemotherapy for advanced NSCLC patients. Our NMA presented preferred ranking probabilities for each treatment to determine which treatment regimen would rank as the best in our cohort of all-comers, as well as in specific subgroups. We further evaluated treatment performance in the first-line setting and in the second-line-or-later setting.

In the NMA of all-comers, the pembrolizumab/chemotherapy combination was found to be more effective than other PFS and OS treatments. When conducting subgroup analyses of treatments in patients grouped by PD-L1 expression levels, different preferences emerged. In the subgroup of patients with high PD-L1 expression ($\geq 50\%$), atezolizumab had the highest probability of ranking as the best treatment for OS when looking at all treatment lines and when looking at only first-line settings. This finding is significant because it contrasts with a previous network meta-analysis. Dafni et al⁵⁴ found that pembrolizumab and pembrolizumab/chemotherapy were the best treatments in the PD-L1 $\geq 50\%$ cohort in the first-line setting, though they did not evaluate atezolizumab monotherapy here. Importantly, our results include more recent data and more trials than previous NMAs, including IMpower110 (comparing atezolizumab and chemotherapy) and KEYNOTE-042 (comparing pembrolizumab and chemotherapy). That said, we did not find any statistically significant OS differences between atezolizumab, atezolizumab/chemotherapy, nivolumab/ipilimumab, pembrolizumab, or pembrolizumab/chemotherapy. In the context of these previous findings, we believe atezolizumab might become the preferred treatment in the first-line setting of patients with high PD-L1 expression ($\geq 50\%$), though this should be interpreted with caution until the IMpower110 trial publishes their final OS results. Furthermore, since pembrolizumab and pembrolizumab/chemotherapy still show similar benefits and have been studied in a greater number of patients, their use in this patient population and treatment line is still acceptable. Given the significant increase in treatment-related adverse events in ICI/chemotherapy combinations, the benefit of combination therapies should be weighed against the considerably higher risk of adverse events. While we did not compare treatments in the second-line or later setting for patients with PD-L1 $\geq 50\%$ expression,

Kim et al⁵⁵ found that nivolumab was the best ranked treatment for this cohort, though they did not find a significant difference between atezolizumab and nivolumab.

In the cohort of patients with intermediate PD-L1 expression (1%-49%), pembrolizumab/chemotherapy combination had overwhelmingly favorable performance over chemotherapy and most other ICIs treatment both in OS and PFS, making it the preferred treatment for this cohort. When evaluating OS in only the first-line setting, pembrolizumab/chemotherapy still ranked the better than chemotherapy and all ICIs it was compared against (atezolizumab/chemotherapy, atezolizumab, and pembrolizumab).

For the cohort of patients with low PD-L1 expression (<1%), the nivolumab/ipilimumab combination had the highest probability of ranking best in terms of OS. While pembrolizumab/chemotherapy had the greatest PFS benefit, it did not differ in a statistically significant way from nivolumab/ipilimumab. When evaluating OS in only the first-line setting, nivolumab/ipilimumab was also found to be the most preferred treatment. It is possible that the PD-L1/PD-1 inhibitors' mechanism of action could result in an influx of inflammatory cells to the cancer site, leading to 'pseudo-progression', as Kazandjian et al⁵⁶ have reported in their study. As such, we believe nivolumab/ipilimumab to be the preferred treatment in patients with low PD-L1 expression (<1%) in the first-line setting. None of the included studies evaluated this treatment in second-line or greater setting. Again, however, it is important to recognize the significantly higher risk of treatment-related adverse events when using combination therapies.

In a network meta-analysis of ICI treatments in the first-line setting of wild-type EGFR/ALK patients, Liu et al⁵⁷ suggested that pembrolizumab/chemotherapy combination seemed to be a more effective regimen for patients with PD-L1 expression of <50%. This supports our findings for patients with intermediate PD-L1 expression (1-49%) but contrasts with our findings for patients with low PD-L1 expression (<1%). As we look at both 1%-49% and <1% in the first-line setting, we consider our findings more specific and are thus one of our strengths in determining the ideal treatment.

We conducted a subgroup analysis of OS in the second-line or later setting, finding that pembrolizumab, atezolizumab, and nivolumab all demonstrated similar benefit over chemotherapy. While there were no significant differences among the three regimens, pembrolizumab had a higher

probability of ranking best. It is a limitation of our study to not stratify second-line results by PD-L1 expression level, and so the clinical usefulness of our rankings for second-line or later settings is limited. We suggest clinicians refer to the network meta-analysis by Kim et al⁵⁵ for treatment preferences by PD-L1 expression subgroups in the second-line or later setting. As this is a rapidly developing field, an updated network meta-analysis looking at second-line or later settings may soon be warranted.

Squamous cell carcinoma is a much more complicated disease, probably because of the influence of tobacco in most of these patients that causes an extremely high rate of mutations and other genetic changes. In contrast, non-squamous cell carcinoma is a less complicated form of the disease that tends to derive from those single driver mutations. Thus, the options for upfront genotyping in squamous NSCLCs are much more limited⁵⁸, and so are the targeted therapies. We re-evaluated the efficacies according to histology type, comparing nivolumab, pembrolizumab/chemotherapy, and atezolizumab/chemotherapy in both squamous and non-squamous cohorts. In the non-squamous cohort, all three ICIs treatments showed statistically significant OS benefit over chemotherapy and, among them, pembrolizumab/chemotherapy evidenced the greatest OS benefits over chemotherapy. In the squamous cohort, only nivolumab and pembrolizumab/chemotherapy evidenced (comparable) benefits over chemotherapy. Identification of the preferred ICI treatments in patients with squamous tumor histology requires further exploration given their limited representation in trials. We hope our findings will encourage future exploration of this issue to find more conclusive evidence of how to best incorporate tumor histology in treatment selection.

Ipilimumab is an anti-CTLA-4 antibody, with a mechanism of action that is distinct from nivolumab but seen to be complementary. According to Larkin et al⁵⁹ and Motzer et al⁶⁰, this combination evidenced longer overall survival in patients with melanoma and renal-cell carcinoma. In our study, we evaluated this combination of two antibodies with different targets indirectly with monotherapy. When all treatment-line settings were assessed, nivolumab/ipilimumab combination therapy did not improve OS over nivolumab monotherapy when compared in all-comers or in patients with PD-L1 \geq 50% and <1%. In only the first-line setting, the combination did improve OS over nivolumab monotherapy when assessed

in all-comers, but not when assessed in patients with PD-L1 $\geq 50\%$. Moreover, the combination had considerably increased the risk of grade-3 or greater treatment-related adverse events. Despite this, we should not stop exploring combination immunotherapy, particularly considering we will need ways to manage cancers which develop resistance to immunotherapy, or to manage patients which may otherwise not respond to monotherapy. The dual immune checkpoint inhibitor combination may indeed be worth exploring, particularly considering it appeared to be the best-ranked treatment for first-line patients with PD-L1 expression of $<1\%$, though there were no nivolumab monotherapy trials to compare it with in this setting.

While durvalumab is only currently only FDA-approved for unresectable Stage III NSCLC based on the phase 3 PACIFIC and CASPIAN trials results, we decided to include this drug into our analysis to evaluate its role in advanced NSCLC⁶¹. While there were only two trials (MYSTIC and ARCTIC Study B) evaluating durvalumab in advanced NSCLC, neither of these showed any benefit over chemotherapy, and so it does not appear to be a promising therapy. While we did not extract the durvalumab/tremelimumab arms from these two studies, they also did not show any statistically significant benefits over chemotherapy in these studies^{41,62}.

The field of immunotherapies in NSCLC is rapidly evolving, with more trials of different ICIs and ICI combination regimens ongoing. One emerging trend is to combine an ICI with bevacizumab and chemotherapy. Bevacizumab is a 'man-made' monoclonal antibody that selectively blocks human VEGF, which theoretically could suppress VEGF's immunomodulatory effects, thereby amplifying the benefits of immunotherapy. This has shown promising results for atezolizumab/bevacizumab/chemotherapy in the IMpower150 trial^{63,64} and for nivolumab/bevacizumab/chemotherapy in the preliminary results from the TASUKI-52 trial⁶⁵. These two trials were not included in this network meta-analysis as our inclusion criteria pre-specified that the comparison treatment had to be chemotherapy, though we recognize our study is at a disadvantage for not doing so.

There are several limitations in our study. First of all, there is no perfect measure of efficacy for ICI treatment. We evaluate both overall survival and progression-free survival, though we focus primarily on results observed in overall survival analyses when recommending preferred

treatments. These two outcomes are important, but they are not the only important measures. For example, health-related quality of life also has value, particularly to patients, as an efficacy measure.

Secondly, we note that we cannot ignore the heterogeneity that results from pooling first-line and second-line or later settings, especially since the immunogenic chemotherapy can sensitize the tumor to checkpoint inhibitor therapy⁶⁶. This might also explain why we often saw greater efficacy when ICI treatments were combined with chemotherapy. Additionally, trials often allowed patients to crossover when disease progression occurs, which could lead to bias and underestimating treatment benefits in our analysis. There is also heterogeneity in pooling results across all PD-L1 expression cohorts. For these reasons, we believe that the results obtained from our subgroup analyses, particularly by PD-L1 expression in only the first-line setting, offer the most clinically meaningful outcomes for informing treatment choice.

Thirdly, we only looked at the effect of PD-L1 expression on outcomes, even though other markers may also be relevant. The meta-analysis and individual patient-level analysis by Yu et al⁶⁷ also used the TMB as predictor for immunotherapy, finding that the joint use of PD-L1 expression and TMB to be a promising predictor of patient survival and response to precision immunotherapy, and the combination of CD8+T-cell TILs, PD-L1 expression, and TMB were reliably associated with prognosis. The independent PD-L1 expression biomarker by itself may, therefore, be inadequate for identifying patients who could derive the greatest therapeutic benefit.

Apart from the limitations mentioned above, we believe our study also has several strengths. Recently, several NMA evaluated the efficacy and/or safety of ICIs treatments for advanced NSCLC patients, but most of them only estimated the first-line setting^{54,57}, and only one study has included second-line setting trials into their analysis⁵⁵. Our study included multiple subgroup analyses, which reduces heterogeneity and provides more clinically useful data for treatment selection based on patient characteristics. Furthermore, various other network meta-analyses performed analysis of PD-L1 expression subgroups differently: one based on $<1\%$, 1% , $\geq 5\%$, and $\geq 50\%$ groupings⁶⁸, one in only the PD-L1 expression $<1\%$ subgroup⁶⁹. In contrast, we divided all-comers into three cohorts by PD-L1 expression $\geq 50\%$, 1% - 49% , and $<1\%$.

In this way, we avoided the risk of overlapping and while also providing more practical evidence. We also believe our results to be more comprehensive, given the large number of included trials and most recent results, as well as the number of subgroup analyses we have performed to reduce the heterogeneity in our analysis.

Conclusions

Overall, pembrolizumab/chemotherapy combination was found to be the most effective therapy in the cohort of all-comers. When we grouped patients by different characteristics, the prevailing treatments were diverse. As for the different PD-L1 expression cohorts, we would suggest that atezolizumab, the pembrolizumab/chemotherapy combination, and the nivolumab/ipilimumab combination to be the preferred treatments for the PD-L1 \geq 50%, PD-L1 1-49%, and PD-L1<1% cohorts, respectively. However, it is important to note that these are based on results from use in both first and second-line or later settings, though these same treatment preferences emerged when we evaluated only studies in the first-line setting. When we performed subgroup analysis by tumor histology, we found that pembrolizumab/chemotherapy performed best in non-squamous cancers while nivolumab monotherapy and pembrolizumab/chemotherapy had similar advantages over chemotherapy in squamous cancers. As for safety outcomes, all four ICI monotherapies reduced the risk of grade 3 or greater treatment-related adverse events compared to chemotherapy, with nivolumab proving the best. With the addition of chemotherapy or a CTLA-4 antibody to any ICI treatment, the risk of treatment-related adverse events increased in a considerable and statistically significant way. As such, in clinical decision-making, we should also consider patient and tumor characteristics, tolerance, and safety. Currently, while more researchers are working on testing new ICIs and combination regimens, there is still a long way to go in determining the best therapeutic regimen for different patients, and we encourage more research focusing on identifying ideal biomarkers to aid in prognostication and treatment selection.

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Availability of data and material

The data of the study are available from the corresponding author.

Conflict of Interests

The Authors declare that they have no conflict of interests.

Code availability

R codes are available from the corresponding author.

Authors' contributions

All authors had full access to all the data in this study and take responsibility for integrity of the data and the accuracy of the data analysis.

SW and YK are the corresponding authors and primary investigators; DW, LGS, and FS contributed equally and share the first authorship; DW, YK and SW conceived of and designed the study; SW, FS and YK acquired funding; DW, LGS, TQ and JW supervised data collection; DW, LGS, and FS analyzed and interpreted the data; DW and LGS wrote the original draft of the manuscript. All authors contributed to reviewing and editing the manuscript.

Conflict of Interests

The authors declare that they have no conflict of interest.

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