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Efficacy and safety of anti-PD-1/PD-L1 in combination with chemotherapy or not as first-line treatment for advanced non-small cell lung cancer: A systematic review and network meta-analysis

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Abstract

Background: The aim of this network meta-analysis (NMA) was to evaluate the efficacy and safety of PD-1/PD-L1 inhibitors, alone or in combination with chemotherapy, as first-line treatment for wild-type advanced non-small cell lung cancer.

Methods: We systematically searched databases, Clinical Trial.gov and included randomized clinical trials focusing on advanced NSCLC using PD-1/PD-L1 inhibitors as first-line treatment. Hazard ratio for overall survival and progression-free survival, odds ratio for any-cause high-adverse events (grade 3 or higher) were documented according to Bayesian NMA. Subgroup analysis was performed according to PD-L1 level and histology.

Results: Thirteen trials including 9154 patients were included. In the PD-L1 non-selective cohort, chemotherapy in combination with pembrolizumab and atezolizumab, respectively, were significantly better than any other treatment strategies in both OS benefit (HR = 0.63; HR = 0.85) and PFS benefit (HR = 0.52; HR = 0.63). In subgroup analysis, pembrolizumab appeared to provide the best OS benefit (HR = 0.67) as well as the best PFS benefit (HR = 0.67) in the PD-L1 ≥ 50% cohort. In contrast, pembrolizumab combined with chemotherapy exhibited the best OS benefit in the PD-L1 < 50% cohort. Furthermore, OS benefit from pembrolizumab plus chemotherapy was more obvious in nonsquamous patients (HR = 0.56). Additionally, pembrolizumab plus chemotherapy was associated with fewer adverse events than other chemotherapy combination strategies.

Conclusions: In the first-line treatment, chemotherapy plus pembrolizumab or atezolizumab could enhance efficacy compared with chemotherapy alone or other PD-1/L1-based treatment strategies, especially in the nonsquamous population. Furthermore, pembrolizumab plus chemotherapy guarantees reliable security simultaneously, which may be the optimal treatment strategy for patients with major advanced NSCLC.

KEYWORDS
carcinoma, immune checkpoint inhibitors, network meta-analysis, non-small cell lung

INTRODUCTION

Among all the causes of cancer deaths, lung cancer remains the first,[1] and non-small cell lung cancer (NSCLC) accounts for approximately 85% of patients with lung primary carcinoma. NSCLC is hard to diagnose in the early stages, and the 5-year survival of advanced or metastatic NSCLC patients is low with around 5%[2] receiving traditional treatment of chemotherapy-based strategies. Recently, tyrosine kinase inhibitors (TKIs) are being used more for mutated advanced NSCLC patients, and have better benefits than chemotherapy in improving longer-time-to-event outcomes.

However, more than 50% patients are diagnosed with wild-type NSCLC and to date an efficient treatment strategy has been lacking in these patients. The recent introduction of immune checkpoint inhibitors (ICIs) has improved the survival results for patients with advanced wild-type NSCLC, and improved this unacceptable situation. The programmed cell death 1/anti-programmed death ligand 1(PD-1/L1) pathway, previously detected in a variety of malignant tumors, plays an important role in fighting against tumors by regulating the function of autoimmunity.[3,4] Anti-PD-(L) 1 monoclonal antibodies are one kind of ICI gradually being approved for the treatment of NCSLC and have been reported to perform satisfactory clinical effects.[5–7]

Although there are many clinical trials which have evaluated the efficacy and safety of immunotherapy or chemo-immunotherapy compared with chemotherapy, many of which have suggested a hopeful increase in overall survival (OS) and progression-free survival (PFS)[8–11](Impower130; Keynote 042; Keynote189), direct comparison evidence between immunotherapy-based agents is insufficient. There have been some meta-analyses which have evaluated the efficacy and safety among various anti-PD (L) 1 drugs,[12,13] but some eligible trials have not been included, and data of some included individual studies are out of date.

The objective of this network meta-analysis (NMA) was to summarize and incorporate up-to-date information of eligible studies using PD-1/L1 inhibitors as front-line treatment, evaluating the optimal treatment strategies for advanced NSCLC.

METHODS

The referred reporting items for systematic reviews and meta-analysis (PRISMA) extension statement for network meta-analysis[14] was followed to perform this NMA.

Data sources and searches

English and Chinese databases were systematically searched before August 17, 2020 in all languages, involving PubMed, the Cochrane Library, CBM, CNKI, Wang Fang, and VIP. We also screened ClinialTrials.gov in case of missing ongoing studies. The keywords used for searching the databases included carcinoma, non-small cell lung, NSCLC, PD-1, PD-L1, checkpoint inhibitor, nivolumab, pembrolizumab, atezolizumab, ipilimumab, avelumab, tremelimumab, durvalumab, advanced, 1st-line, first-line, untreated, chemo-naive, etc. In addition, we supplemented Camel study and Impower 132 study before data analysis. The detailed retrieval strategy in the Cochrane Library is presented in Table S1.

Study selection

We included phase II/III randomized controlled clinical trials which met the following criteria: (1) Advanced, metastatic or recurrent NSCLC. (2) PD-1/L1 inhibitors alone or combined with chemotherapy as first-line therapy. (3) Reporting survival outcomes including OS, PFS or grade ≥ 3 adverse events (the definition of OS: time from randomization to death from any cause; definition of PFS: time from randomization until disease progression or death from any cause).

The definition and grade of adverse events is on the basis of the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE).

Studies not meeting the above criteria were excluded. Other exclusion criteria were: (1) Patients receiving other therapies as frontline other than PD-1/L1 inhibitor-based agents. (2) Patients with sensitive mutations such as *EGFR* or *ALK* mutation.Titles and abstracts were screened first followed by assessment of the full text. Durations of any follow-up were eligible and updated data were used for analysis.

Data extraction and risk of bias assessment

Detailed information of eligible trials and characteristics of involved patients were extracted, including the study name, publication sources, year of publication, study phase, treatment regimen, stage of NSCLC, histological type, PD-L1 level, hazard ratio (HR) with 95% confidence interval (95%CI) for OS and PFS, times of any cause high-adverse events (≥ grade 3), sample size, patients' medium age, sex and histology distribution, smoking status, Eastern Cooperative Oncology Group (ECOG) performance-status score, central nervous system (CNS) status, and ethnic background.

Cochrane risk of bias tools from seven perspectives were used to perform the assessment of risk of bias of individual studies: (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 bias.

Four investigators (L.W., Y.Y., X. N, X.L) extracted data and assessed the risk of bias of included studies independently. Disagreements were resolved by consulting other authors (B.A.).

Statistical analysis

The primary outcome was OS, the secondary outcomes were PFS and high-AEs, HR with 95% CI for OS and PFS, OR

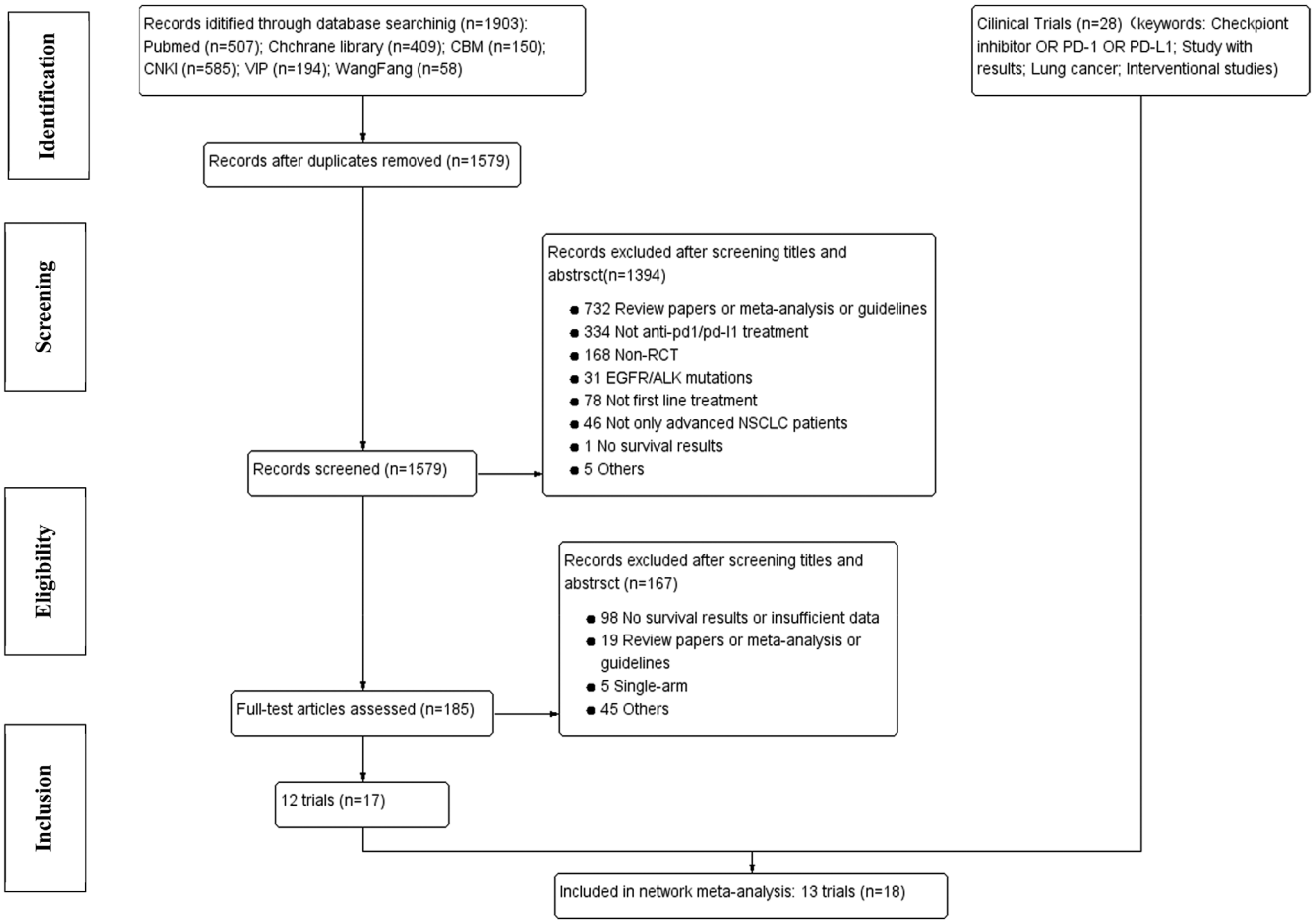

FIGURE 1 Flow diagram of study selection

with 95% CI for grade ≥ 3 AEs were synthesized by Bayesian approach, direct and indirect data were both included in this NMA.

HR was first transformed into the form of lnHR and standard error of lnHR (selnHR). As for head-to-head comparison in two-arm original trials, lnHR and selnHR for OS and PFS were calculated by this formula: $se = (\frac{\ln(HR_{uci}) - \ln(HR_{lci})}{3.92})$, referring to the previously reported methods.[15] In terms of multiarms study, for example, a three-arm study was divided into three direct head-to-head comparisons. Covariance between three comparisons was deemed to be the same, lnHR and selnHR for OS and PFS in the reference group was calculated based on previous methods[15]: $se_b = \sqrt{\sqrt{((se_{k1,b}{}^2 + se_{k2,b}{}^2 - se_{k1,k2}{}^2)/2)}}$*(* b: Reference group; k1/k2: Intervention group).

R software (version 3.5.3) and Stata (version 13.0) were applied to this NMA. In the R software, we established a consistency model in random effect with four Markov chains with package "gemtc" and package "ggplot". For each chain, we used 50 000 iterations and 20 000 sample burnins. By this process, the model was initialized, and subsequent pooled analysis and mixed analysis were performed on the basis of this model. The pooled analysis included direct evidence and showed the relative effects of each intervention compared with chemotherapy, which was visualized by forest plots. The mixed analysis included both direct and indirect evidence and showed the relative effects between any two interventions, which ranked each regimen from best to worst according to outcome measurement and was visualized by the surface under the cumulative ranking curve (SUCRA) values. Stata in random model was used to assess the publication bias by funnel plots and generate network evidence plots according to the number of trials and sample size.

Heterogeneity was evaluated by I-square visualized by forest plots. I^2 value <50% was considered low probability of heterogeneity. In addition, subgroup analysis was carried out according to PD-L1 and histology.

RESULTS

Study selection and characteristics

A total of 1931 records were identified from six online databases (PubMed, the Cochrane library, CBM, CNKI, VIP, Wan Fang) and ClinicalTrials.gov. A total of 185 records

TABLE 1 Characteristics of eligible studies

Study name	Publication	Year	Phase	Stage	Histology	PD-L1 expression	Regimen		OS HR (95%CI)	PFS HR (95% CI)	Adverse events (> = 3 grade)
							Experimental arm	Control arm	Overall	Overall	Experiment/control
Checkmate 026	*NEJM*	2017	III	IV/recurrent	Mix	> = 1%	Nivo 271	Chemo 270	1.17 (0.95–1.43)	1.17 (0.9–1.43)	18% /51%
Keynote 189	JCO	2020	III	IV	NSq	Nonselective	Pembro+Chemo 410	Chemo 206	0.56 (0.45–0.7)	0.48 (0.4–0.58)	71.9%/66.8%
Keynote 407	JCO	2020	III	IV	Sq	Nonselective	Pembro+Chemo 278	Chemo 281	0.71 (0.58–0.88)	0.57 (0.47–0.69)	69.8%/68.2%
Checkmate 227	NEJM	2019	III	IV/recurrent	Mix	Nonselective	1.Nivo+Ipi/Nivo 396/396 2.Nivol+Ipili/Nivol+Chemo 187/177	1.Chemo 397 2.Chemo 186	0.73 (0.64–0.84)(Nivo +ipi vs Chemo)	0.83(0.72–0.96)(Nivo +ipi vs Chemo)	132.8%/36% (Nivo +ipi vs Chemo)
IMpower 130	Lan Onco	2019	III	IV	NSq	Nonselective	Atez+Chemo 451	Chemo 228	0·79 (0·64–0·98)	0·64 (0·54–0·77)	81%/71%
IMpower 131	JTO	2020	III	IV	Sq	Nonselective	Atez+Chemo 343	Chemo 340	0.88 (0.73–1.05)	0.71 (0.60–0.85)	68.0%/57.5%
IMpower 132	JTO	2020	III	IV	NSq	Nonselective	Atez+Chemo 292	Chemo 286	0.81 (0.64–1.03)	0.60 (0.49–0.72)	71.5%/60.6%
Keynote 021G	JTO	2019	II	IIIB/IV	NSq	Nonselective	Pembro+Chemo 60	Chemo 63	0.56 (0.32–0.95	0.53 (0.33–0.86)	40.7%/27.4%
Keynote 024	JCO	2019	III	IV	Mix	> = 50%	Pembro 154	Chemo 151	0.63 (0.47–0.86)	0.50 (0.37–0.68)	31.2%/53.3%
Keynote 042	Lan Onco	2019	III	IV	Mix	> = 1%	Pembro 637	Chemo 636	0·81 (0·71–0·93)	1·07 (0·94–1·21).	18%/41%
MYSTIC	JAMA Onco	2020	III	IV	Mix	Nonselective	Durva/Durva +Treme 369/371	Chemo 352	**0.96 (0.81–1.13)**(Durva/Chemo); **0.94 (0.79–1.10)**(Durva+Treme/ Chemo)	1.05 (0.72–1.53)(Durva +Treme/Chemo)	14.9%/22.9%/33.8%
IMpower 110	NEJM	2020	III	IV	Mix	> = 1%	Atez 277	Chemo 277	0.83 (0.65–1.07)	0.77 (0.63–0.94)	30.1%/52.5%
Camel	Lan Resp Med	2021	III	IIIB/IV	NSq	Nonselective	Camre+Chemo 205	Chemo 207	0.73 (0.53–1.02)	0·60 (0·45–0·79)	69%/98%

Abbreviations: Atez, atezolizumab; Camre, camrelizumab; Chemo, chemotherapy; Durva, durvalumab; Ipi, ipilimumab; JAMA Onco, JAMA Oncology; JCO, journal of clinical oncology; JTO, Journal of Thoracic Oncology; Lan Onco, Lancet Oncology; Lan Resp Med, Lancet Respiratory Medicine; Lan, Lancet; Mix, nonsquamous and squamous; NEJM, New England Journal of Medicine; Nivo, nivolumab; NSq, nonsquamous; Pembro, pembrolizumab; Sq, squamous; Treme, tremelimumab.

TABLE 2 Patient characteristics of the included studies

Study name	Total *N*	PD-L1 level (experiment/control)			Age (median) (experiment/Control)	Male (n,%) (experiment/control)
		≥50%	1%–50%	≤1%		
Checkmate 026	541	88/126	208/210	0	63.0/65.0	184(67.9)/148(54.8)
Keynote 189	616	132/70	128/58	127/63	65.0/63.5	254(62.0)/109(52.9)
Keynote 407	559	73/73	103/104	95/99	65.5/65.0	220(79.1)/235(83.6)
Checkmate 227	1739	205/214/192 (Nivo+Ipi/Nivo/Chemo)	191/182/205 (Nivo+Ipi/Nivo/Chemo)	187/177/186 (Nivo+Ipi/Nivo+Chemo/Chemo)	64.0/64.0/64.0 (Nivo+Ipili/Nivo/Chemo) 63.0/64.0/64.0 (Nivo+Ipi/Nivo+Chemo/Chemo)	255 (64.4)/272 (68.7)/260 (65.5) (Nivo+Ipili/Nivo/Chemo) 138(73.8)/130(73.4)/125(67.2) (Nivo+Ipili/Nivo+Chemo/Chemo)
IMpower 130	679	88/42	128/65	235/121	64.0/65.0	266(59.0)/134(58.8)
IMpower 131	683	47/44	136/125	160/171	65.5/65.0	279(81.0)/278(82.0)
IMpower 132	578	25/20	63/73	88/75	64.0/63.0	192(65.8)/192(67.1)
Keynote 021G	123	20/17	19/23	21/23	62.5/63.2	22(37.0)/26(41.0)
Keynote 024	305	125/124	0	0	64.5/66.0	92(59.7)/95(62.9)
Keynote 042	1273	299/300	338/337	0	63.0/63.0	450(70.6)/452(71.0)
MYSTIC	1092	118/108/107 (Durva/Durva+Treme/Chemo)	NA	95/76/83 (Durva/Durva+Treme/Chemo)	64.0/65.0/64.5	113 (69.3) /118 (72.4) /106 (65.4)
IMpower 110	554	107/98	170/179	0	64.0/65.0	196(70.8)/196(69.7)
Camel	412	49/69	108/97	30/20	59.0/61.0	146(71.2)/149(72)

Study name	Nonsquamous (n,%)(Experiment/Control)	Never Smoked (n,%)(Experiment/Control)	ECOG 0(n,%)	CNS metastasis (n,%)	Asia
Checkmate 026	205 (76)/206(76)	30 (11)/29 (11)	85 (31)/93 (34)	33 (12)/36 (13)	30(11)/17 (6.3)
Keynote 189	410 (100)/206(100)	48 (11.7)/25 (12.1)	186 (45.4)/80 (38.8)	73 (17.8)/35 (17)	4 (1)/6 (2.9)
Keynote 407	0/0	22 (7.9)/19 (6.8)	73 (26.3)/90 (32.0)	20 (7.2)/24 (8.5)	54 (19.4)/52 (18.5)
Checkmate 227	279 (70.5)/279 (70.5)/281 (70.8) (Nivo+Ipi/Nivo/Chemo) 140 (74.9)/134 (75.7)/140 (75.3) (Nivo+Ipi/Nivo+Chemo/Chemo)	56 (14.1)/50 (12.6)/51 (12.8) (Nivo+Ipi/Nivo/Chemo) 23 (12.3)/27 (15.3)/27 (14.5) (Nivo+Ipi/Nivo+Chemo/Chemo)	135 (34.1)/142 (35.9)/134 (33.8) (Nivo+Ipi/Nivo/Chemo) 69 (36.9)/59 (33.3)/57 (30.6) (Nivo+Ipi/Nivo+Chemo/Chemo)	41 (10.4)/42 (10.6)/40 (10.1) (Nivo+Ipi/Nivo/Chemo) 23 (12.3)/16 (9.0)/11 (5.9) (Nivo+Ipi/Nivo+Chemo/Chemo)	81 (20.5)/66 (16.7)/81 (20.4) (Nivo+Ipi/Nivo/Chemo) 40 (21.4)/36 (20.3)/43 (23.1) (Nivo+Ipi/Nivo+Chemo/Chemo)
IMpower 130	451 (100)/228 (100)	48 (11)/17(7)	189 (42%)/91 (40%)	NG	12 (3)/3(1)
IMpower 131	0/0	32 (9.3)/23(6.8)	115 (33.5)/110 (32.4)	NG	41 (12.0)/37 (10.9)
IMpower 132	292 (100)/286 (100)	37 (12.7)/30(10.5)	126 (43)/114 (40)	NG	71 (24.3)/65 (22.7)
Keynote 021G	60 (100)/63 (100)	15 (25)/9(14)	24 (40) /29 (46)	9 (15)/6 (10)	5 (8)/5 (8)
Keynote 024	125 (81.2)/124 (82.1)	5 (3.2) /19(12.6)	54 (35.1)/53 (35.1)	18 (11.7)/10 (6.6)	21(13.6) 19 (12.6)
Keynote 042	394 (62)/388(61)	142 (22)/140 (22)	198 (31)/192 (30)	35 (5)/35 (5)	85 (29)/185 (29)
MYSTIC	111 (68.1)/ 110 (67.5)/110 (67.9) (Durva/Durva+Treme/Chemo)	24 (14.7)/ 25 (15.3)/21 (13.0) (Durva/Durva+Treme/Chemo)	57 (35.0)/65 (39.9)/70 (43.2) (Durva/Durva+Treme/Chemo)	NG	59 (36.2)/50 (30.7) /47 (29.0) (Durva/Durva+Treme/Chemo)
IMpower 110	277 (100)/277 (100)	37 (13.4)/35 (12.6)	97 (35.0)/102 (36.8)	NG	45 (16.2)/30 (10.8)
Camel	205 (100)/207 (100)	NA/NA	48 (23.4)/36 (17.5)	10 (5)/5 (2)	NG

Abbreviations: Camre, camrelizumab; Chemo, chemotherapy; Durva, durvalumab; Ipi, ipilimumab; Nivo, nivolumab; Treme, tremelimumab.

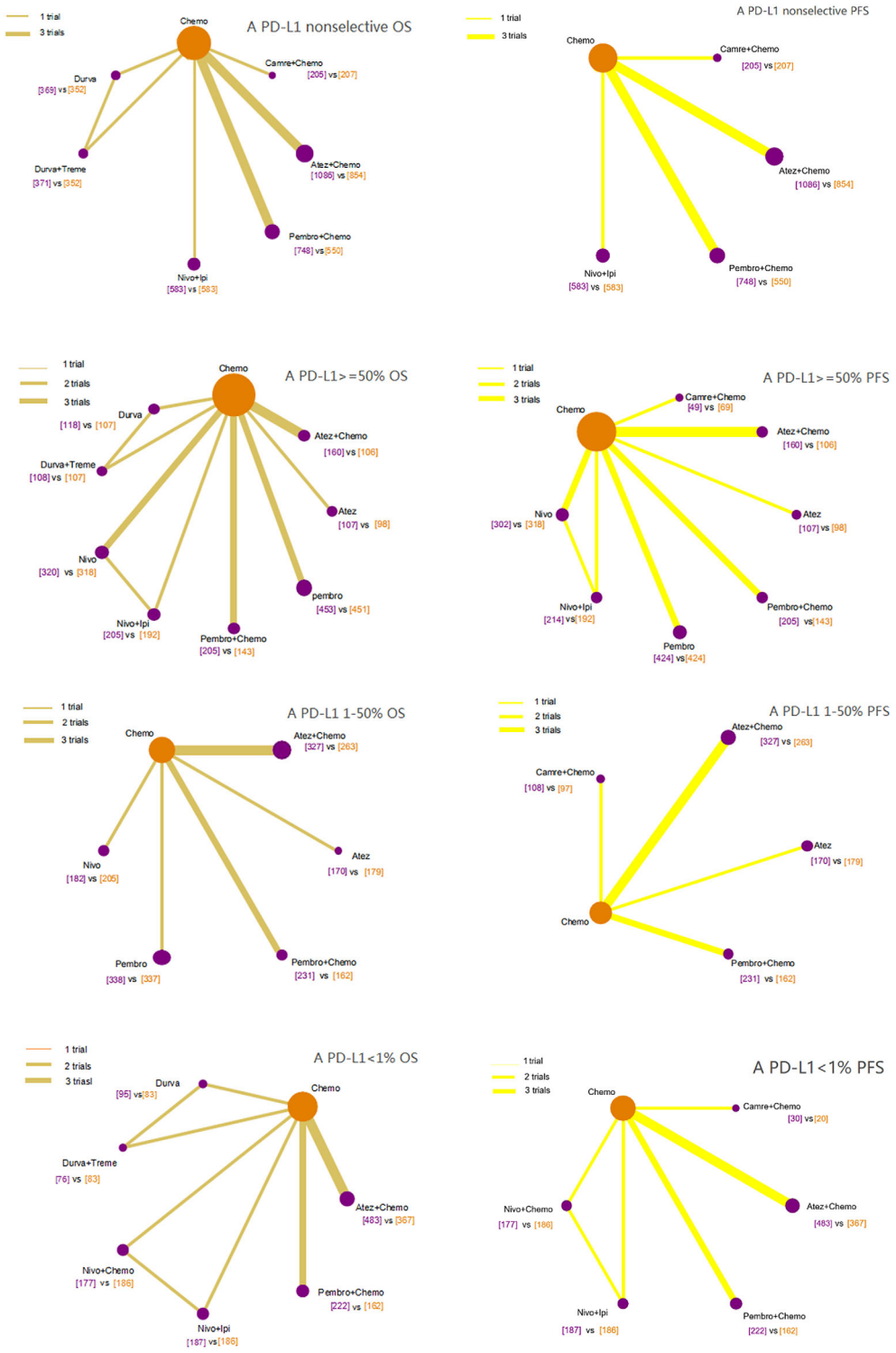

FIGURE 2 Network evidence plots. All groups were included (for example, "A PD-L1 nonselective OS" meant the OS analysis in all patients without PD-L1 section; "A PD-L1 nonselective PFS" meant the PFS analysis in all patients without PD-L1 section; "A PD-L1 >= 50% OS" meant the OS analysis in PD-L1 > = 50% cohort; so as others)

were reviewed for full-text assessment after excluding duplicates and screening for titles and abstracts (Figure 1). Eventually, 13 trials were included in the NMA.[8–11,16–29] The detailed information on patients involved in the study are shown in Tables 1 and 2. Overall, 9154 patients were enrolled in 11 different treatment strategies: chemotherapy (Chemo), nivolumab (Nivo), pembrolizumab plus chemotherapy (Pembro+Chemo), nivolumab plus ipilimumab (Nivo+Ipi), nivolumab plus chemotherapy (Nivo+Chemo), atezolizumab plus chemotherapy (Atez+Chemo), pembrolizumab (Pembro),

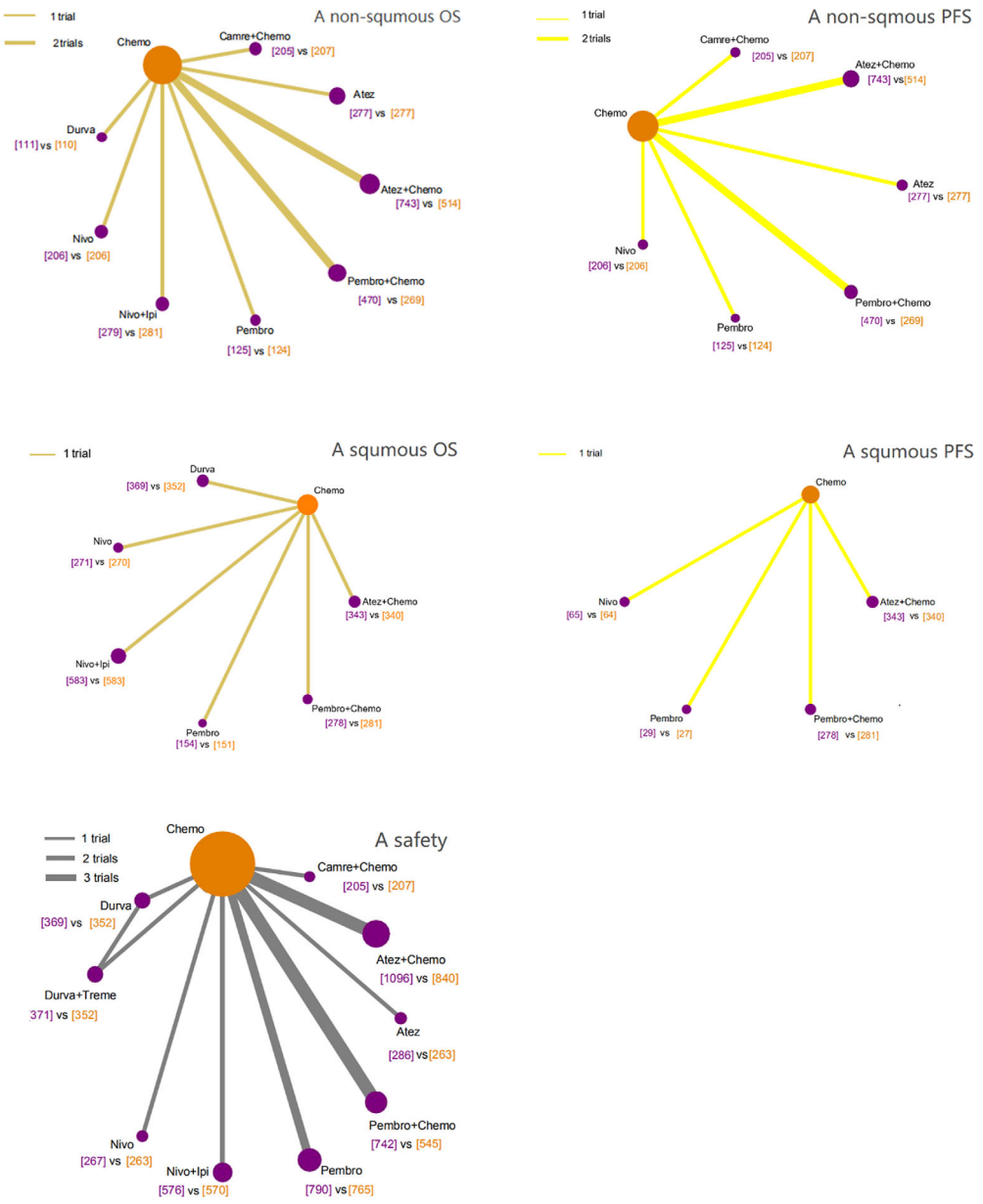

FIGURE 2 (Continued)

durvalumab (Durva), durvalumab plus tremelimumab (Durva +Treme), atezolizumab (Atez), camrelizumab plus chemotherapy (Camre+Chemo).

In general, all studies were phase III random clinical control trials apart from Keynote 021G.[16] Most of the studies included were head-to-head trials apart from Checkmate 227[24,25] and MYSTIC.[29] Six trials enrolled both nonsquamous and squamous NSCLC patients: Checkmate 026,[20] Checkmate 227, Keynote 024,[18,19] Keynote 042,[10] MYSTIC, IMpower 110[21]; five trials focused only on nonsquamous NSCLC patients: Keynote 189,[8,9] IMpower 130,[11] Keynote 021G, IMpower 132,[23] Camel,[28] with two trials focusing on only squamous NSCLC patients. PFS was final analysis in all included studies, most OS analysis was final except Keynote 042, IMpower130 and Camel. Bias assessment is shown in Figure S1.

Primary analysis for OS and PFS in PD-L1 nonselective NSCLC patients

Seven treatments were included for OS and PFS in patients with any PD-L1 level (Figure 2). Pooled direct comparison results between immunotherapy or immunotherapy-combination therapy and standard chemotherapy are shown as forest plots (Figure 3). Pooled mixed comparison results involving all included treatment agents are shown in ranking plots (Figure 4) and league-tables (Figure 5).

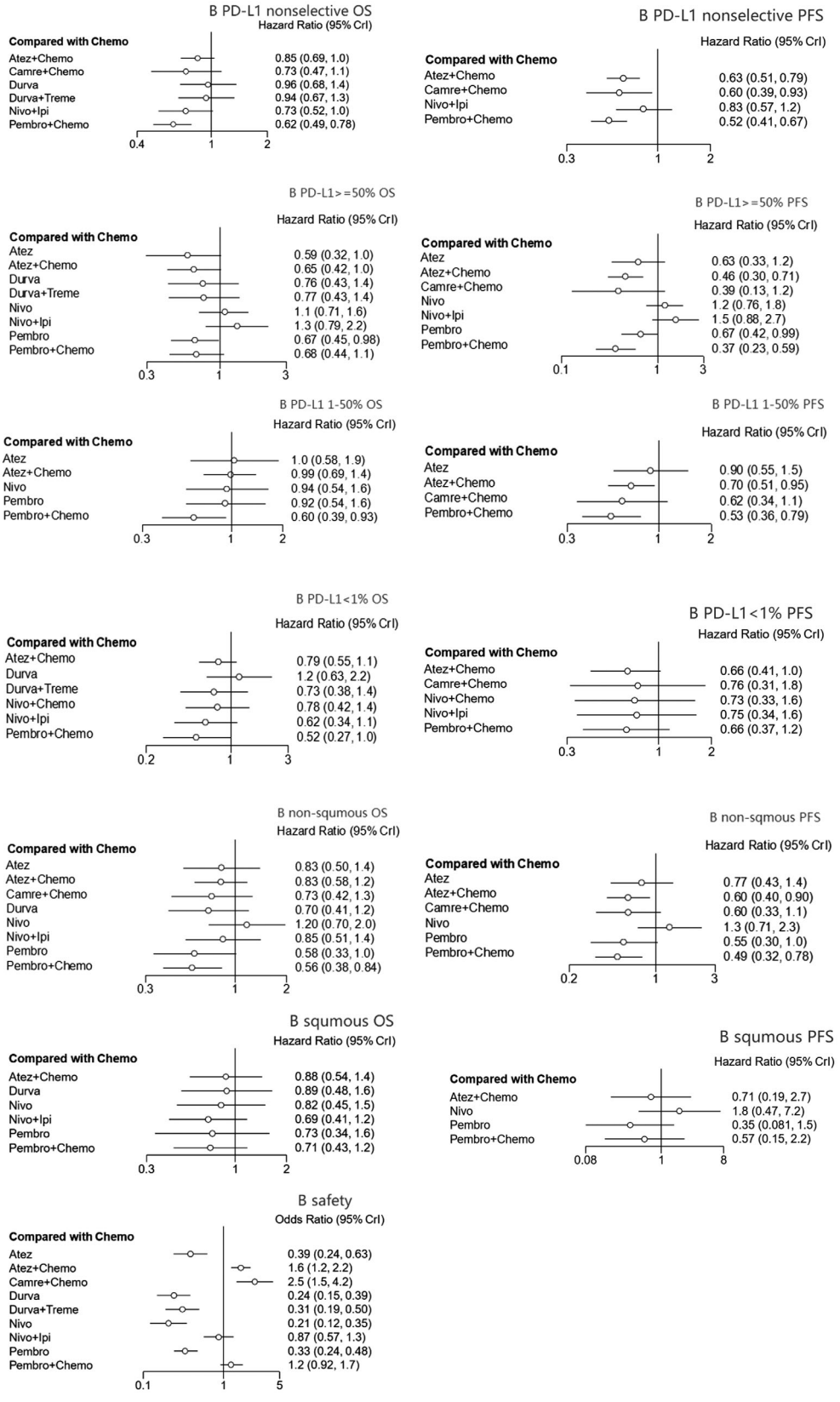

FIGURE 3 Forest plots of pooled direct comparison. "Chemotherapy" was the reference group, the hazards ratio/odds ratio of "intervention group" to "chemotherapy" were provided. (all groups were included, for example, "B PD-L1 nonselective OS" meant the OS analysis in all patients without PD-L1 section, so as others)

In terms of OS, immunotherapy combination therapy seemed to exhibit better benefit than chemotherapy alone. Pembro+Chemo (HR = 0.62, 95% CI: 0.49 to 0.78) and Atez+Chemo (HR = 0.85, 95% CI: 0.69 to 1) yielded superior OS benefit over traditional chemotherapy. Furthermore Pembro+Chemo obtained greater OS benefit

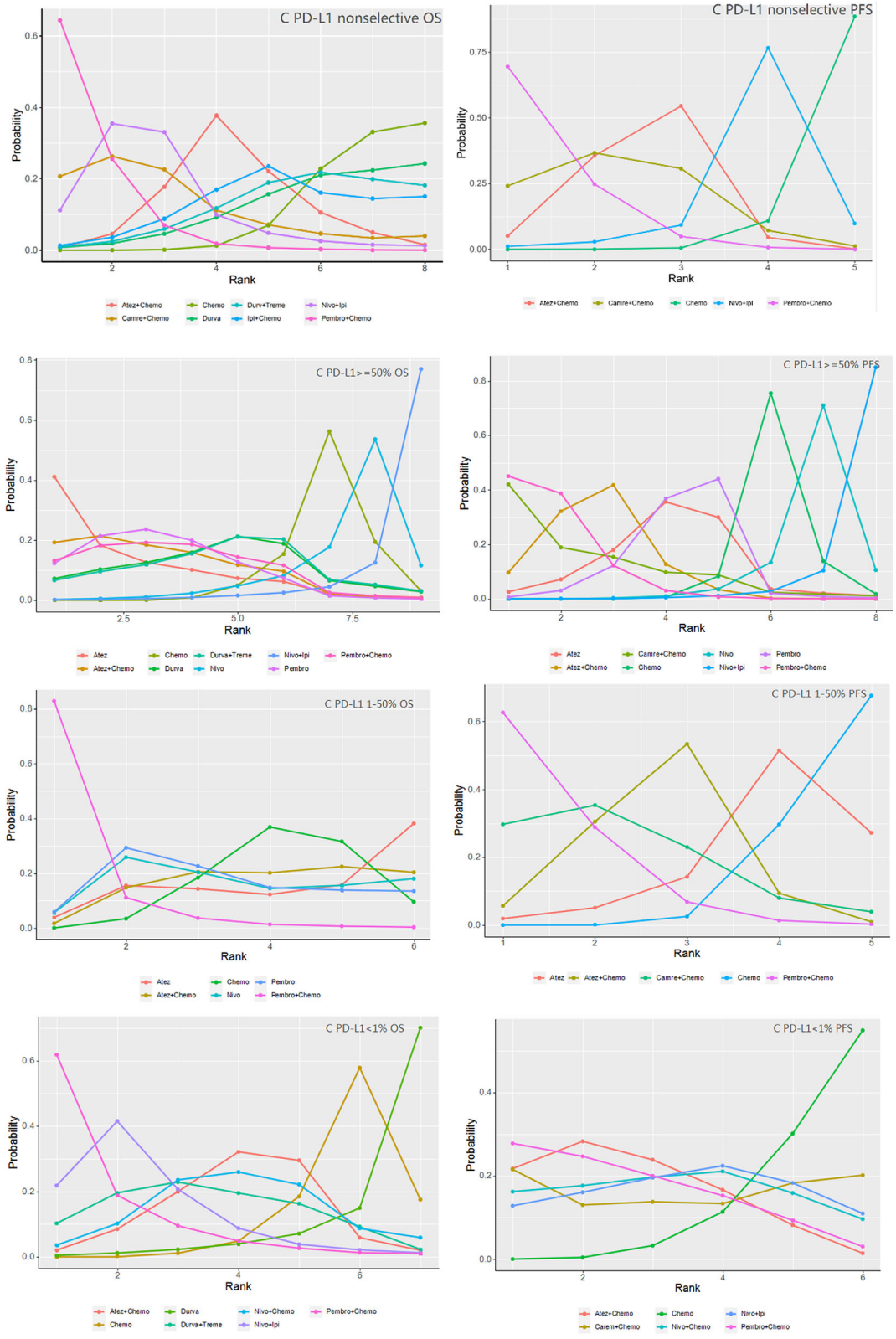

FIGURE 4 Ranking plots of pooled mixed comparison, which show the probability of treatment agents to be ranked at first, second, third … and the last (all groups were included, for example, "C PD-L1 nonselective OS" meant the OS analysis in all patients without PD-L1 section, so as others)

than Atez+Chemo (HR = 0.74, 95% CI: 0.54 to 1). In addition, Pembro+Chemo showed the best OS benefit versus other included treatment agents including Durva (HR = 0.65, 95% CI: 0.43 to 0.97), Durva+Treme (HR = 0.67, 95%CI: 0.43 to 0.99). Bayesian ranking profiles (Figure 4) suggested that Pembro+Chemo was most likely to be ranked first for

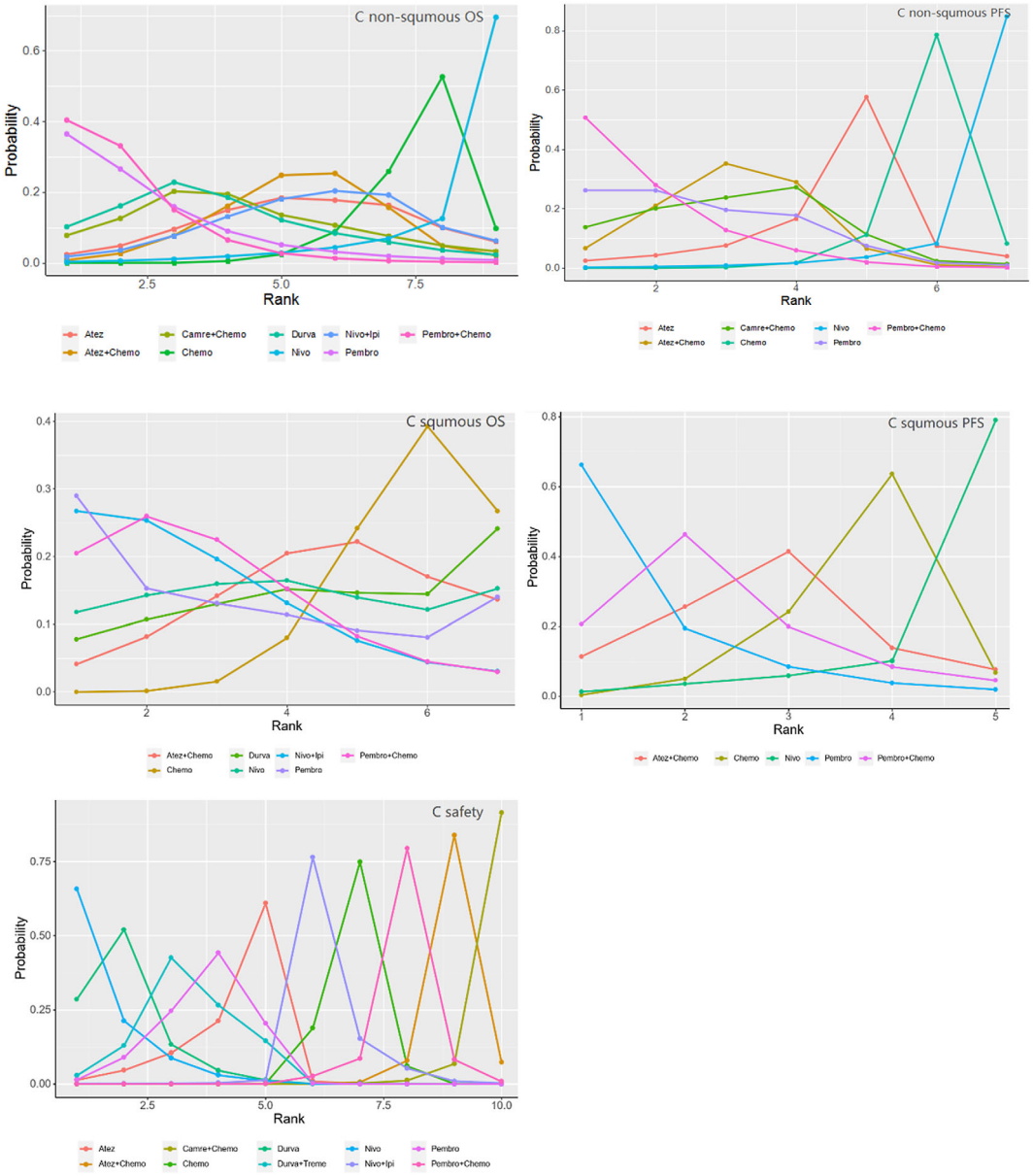

FIGURE 4 (Continued)

prolonging OS (probability = 65%) in PD-L1 expression non-selective NSCLC patients.

As for PFS, immunotherapy combination therapy was also perceived to obtain greater benefit than chemotherapy. Pembro+Chemo (HR = 0.52, 95% CI: 0.41 to 0.67), Atez+Chemo (HR = 0.63, 95% CI: 0.51 to 0.79), Camre+Chemo (HR = 0.6, 95% CI: 0.39 to 0.93) were significantly better than chemotherapy alone in improving PFS. No significant differences were noted between these three advantageous strategies. Pembro+Chemo also showed better PFS upon comparison with Nivo+Ipi (HR = 0.63, 95% CI: 0.41,0.98). However, Bayesian ranking profiles suggested that the pembrolizumab combination strategy should possibly be ranked first to offer best PFS (probability = 69%).

Subgroup analysis for OS and PFS according to PD-L1 level and histology

PD-L1 ≥ 50%

Ten treatments were included in this cohort. As for OS, mono-immunotherapy and immunotherapy combination treatment strategies were discerned to provide better OS benefit. Pembro (HR = 0.67, 95% CI: 0.45 to 0.98) and Atez (HR = 0.59, 95% CI: 0.32 to 0.98) showed a significant benefit compared with Chemo in OS comparison. In addition, Atez+Chemo (HR = 0.65, 95% CI = 0.42 to 0.99) was better than Chemo alone in prolonging OS. No significant differences were found between these three superior agents. Bayesian ranking profiles (Figure 4) suggested that Atez was most likely to be ranked first

(probability = 41%) for OS benefit in PD-L1 ≥ 50% advanced NSCLC patients, followed by Atez+Chemo (probability = 19%) and Pembro alone (probability = 12%).

When it came to PFS, monoimmunotherapy and immunotherapy combination treatment strategies were also perceived to provide better PFS benefit. Pembro (HR = 0.67, 95% CI: 0.42 to 0.99) exhibited superior PFS benefit compared with Chemo alone; Pembro+Chemo (HR = 0.36, 95% CI: 0.23 to 0.59) was similar to Atez+Chemo (HR = 0.46, 95% CI: 0.3 to 0.71) in providing better PFS versus Chemo. There was no apparent benefit difference between these three advantageous strategies. Bayesian ranking profiles indicated that Pembro+Chemo was most likely to be ranked first to offer the best PFS (probability = 45%).

PD-L1 1%–50%

In total, seven treatments were included. In terms of OS, among all the regimens, only Pembro+Chemo (HR = 0.60, 95% CI: 0.39 to 0.93) was significantly better than Chemo in OS comparison. Bayesian ranking profiles suggested that Pembro+Chemo was most likely to be ranked first (probability = 83%) for OS benefit.

As for PFS, Pembro+Chemo (HR = 0.53, 95% CI: 0.36 to 0.79), Atez+Chemo (HR = 0.7, 95%CI: 0.51 to 0.95) was significantly better than Chemo in improving PFS, and no significant difference was found between these two regimens (HR = 1.3, 95%CI: 0.8 to 2.14). Bayesian ranking plots suggested that Pembro+Chemo was most likely to be the best regimen for increasing PFS (probability = 63%) compared with any other included treatment agents.

PD-L1 < 1%

Eight treatments were included. Being similar to the results of OS analysis in PD-L1 1%–50% cohort, Pembro+Chemo was also the only strategy superior to Chemo in prolonging OS in the PD-L1 negative cohort. The remainder of the regimens including monoimmunotherapy and doublet immunotherapy agents exhibited similar benefit with chemotherapy alone in OS comparison. Bayesian ranking plots suggested that Pembro+Chemo was most likely to be ranked first for best OS (probability = 62%).

With regard to PFS, all strategies included showed similar benefit. Bayesian ranking plots also suggested that Pembro+Chemo appeared to be ranked first to improve PFS (probability = 28%).

Nonsquamous NSCLC

For nonsquamous advanced NSCLC patients, nine treatments were included. With regard to OS, all included regimens showed similar efficacy except Pembro+Chemo (HR = 0.56, 95% CI: 0.38 to 0.84) and Pembro alone (HR = 0.58, 95% CI: 0.33 to 1). No significant difference was noted between these two strategies. Pembro+Chemo and Pembro alone appeared to be ranked in the top two for OS benefit, with overall probability at 40% and 36%, respectively.

As for PFS, among all included strategies, Pembro+Chemo (HR = 0.56, 95% CI: 0.38 to 0.84), Atez+Chemo (HR = 0.6, 95% CI: 0.4 to 0.9), Pembro (HR = 0.58, 95 CI: 0.33 to 1) were superior to Chemo alone in PFS improvement. Bayesian profiles suggested Pembro+Chemo was mostly likely to be the best regimen for increasing PFS (probability = 51%).

Squamous NSCLC

Seven treatments were included in squamous NSCLC patients. All treatment strategies included showed no significant difference according to OS benefit and PFS benefit. Bayesian ranking profiles indicated that Pembro was most likely to be the best regimen for prolonging both OS (probability = 28%) and PFS (probability = 65%).

Safety analysis

Ten treatments in 13 trials were included. Monoimmunotherapy and dual-immunotherapy appeared to show a significantly lower hazard ratio than Chemo alone in terms of the incidence of any cause grade ≥ 3 adverse events, including Atez (OR = 0.39, 95% CI: 0.24, 0.63), Durva (OR = 0.24, 95% CI: 0.15, 0.39), Nivo (OR = 0.21, 95% CI: 0.12, 0.35), Pembro (OR = 0.33, 95% CI: 0.24, 0.47), Durva +Treme (OR = 0.31, 95% CI: 0.19 to 0.5), and there was no significant difference between these agents. The immunochemo combination strategy appeared to show a higher risk of causing adverse events apart from Pembro +Chemo (OR = 0.81, 95% CI: 0.57 to 1.1). Bayesian ranking plots suggested that Nivo was most likely to be ranked first not to cause adverse events (probability = 67%); Additionally, Pembro+Chemo was most likely to be ranked first to show the least probability of causing adverse events among all immunochemotherapy agents.

Heterogeneity analysis and publication bias

The result of heterogeneity analysis was shown by I-square value and forest (Figure S2). Generally, no obvious heterogeneity (I^2 < 50%) was found in the primary OS analysis and other subgroup analysis. In addition, funnel plots provided in the appendix (Figure S3) suggested that no obvious publication bias existed.

DISCUSSION

In this NMA, we provide up-to-date information of first-line phase II/III randomized studies evaluating immunotherapy

Network comparision of PFS in non-selective PD-L1 patients

Ate+Chemo	0.95(0.58, 1.54)	**1.58(1.27, 1.97)**	~	~	1.31(0.85, 2.02)	0.83 (0.6, 1.15)
	Carem+Chemo	**1.67(1.08, 2.57)**	~	~	1.38(0.78, 2.43)	0.87 (0.53, 1.43)
Atez+Chemo		**Chemo**	~	~	0.83 (0.57, 1.2)	**0.52 (0.41, 0.67)**
1.16 (0.72, 1.88)	**Camre+Chemo**		**Durva**	~	~	~
0.85 (0.69, 1)	0.73 (0.47, 1.13)	**Chemo**		**Durva+Treme**	~	~
0.88 (0.59, 1.31)	0.76 (0.44, 1.31)	1.04 (0.74, 1.46)	**Durva***		**Nivo+Ipi**	**0.63 (0.41, 0.98)**
0.9 (0.6, 1.34)	0.77 (0.45, 1.34)	1.06 (0.76, 1.5)	1.02 (0.73, 1.44)	**Durva+Treme***		**Pembro+Chemo**
0.93 (0.62, 1.38)	0.8 (0.46, 1.39)	1.1 (0.78, 1.55)	1.06 (0.65, 1.72)	1.03 (0.64, 1.68)		
1.16 (0.78, 1.71)	1 (0.58, 1.71)	1.37 (0.98, 1.91)	1.31 (0.81, 2.12)	1.29 (0.8, 2.08)	**Nivo+Ipi**	
1.35 (1, 1.86)	1.16 (0.72, 1.92)	**1.6 (1.28, 2.04)**	**1.53 (1.03, 2.34)**	**1.5 (1.01, 2.3)**	1.17 (0.79, 1.77)	**Pembro+Chemo**

Network comparision of OS in non-selective PD-L1 patients

Network comparision of PFS in PD-L1≥50% patients

Atez	0.74 (0.34, 1.57)	0.62 (0.17, 2.22)	1.59 (0.84, 3)	~	~	1.89 (0.87, 4.05)	**2.46 (1.05, 5.7)**	1.06 (0.48, 2.2)	0.58 (0.26, 1.28)
	Atez+Chemo	0.85 (0.26, 2.8)	**2.16 (1.41, 3.33)**	~	~	**2.57 (1.4, 4.72)**	**3.34 (1.65, 6.77)**	1.44 (0.77, 2.57)	0.79 (0.42, 1.51)
		Camre+Chemo*	2.5550.84, 7.82)	~	~	3.04(0.92,10.03)	**3.95(1.13,13.71)**	1.69 (0.51, 5.54)	0.93 (0.28, 3.14)
Atez			**Chemo**	~	~	1.19 (0.76, 1.82)	1.55 (0.88, 2.69)	**0.67 (0.42, 0.99)**	**0.37 (0.23, 0.59)**
0.9(0.42,1.92)	**Atez+Chemo**			**Durva**	~	~	~	~	~
~	~	**Camre+Chemo**			**Durva+Treme**	~	~	~	~
0.59(0.32,0.98)	**0.65(0.42,0.99)**	~	**Chemo**			**Nivo**	1.3 (0.74, 2.28)	0.56 (0.3, 1.01)	**0.31 (0.16, 0.59)**
0.78(0.33, 1.81)	0.86(0.42,1.79)	~	1.32(0.73, 2.35)	**Durva***			**Nivo+Ipi**	**0.43 (0.21, 0.85)**	**0.24 (0.11, 0.49)**
0.77 (0.32, 1.8)	0.85(0.41,1.77)	~	1.3 (0.72, 2.32)	0.99(0.55, 1.76)	**Durva+Treme***			**Pembro**	0.55 (0.3, 1.07)
0.54(0.26, 1.15)	0.6(0.34,1.11)	~	0.92(0.62, 1.41)	0.7 (0.35, 1.44)	0.7 (0.35, 1.47)	**Nivo**			**Pembro+Chemo**
0.44 (0.2, 1)	**0.49(0.25,0.97)**	~	0.75(0.45, 1.27)	0.57(0.26, 1.25)	0.57(0.27,1.27)	**0.82(0.48,0.35)**	**Nivo+Ipi**		
0.89(0.43, 1.85)	0.98(0.55,1.77)	~	**1.5 (1.02, 2.24)**	1.14(0.57, 2.31)	1.16(0.57,2.34)	1.64(0.92, 2.85)	**2.01(1.05,3.83)**	**Pembro**	
0.86 (0.4, 1.86)	0.96(0.52,1.8)	~	1.47(0.94, 2.29)	1.11(0.54, 2.33)	1.13(0.54,2.35)	1.6 (0.86, 2.88)	1.96(0.98, 3.85)	0.98(0.54,1.76)	**Pembro+Chemo**

Network comparision of OS in PD-L1≥50% patients

Network comparision of PFS in PD-L1 1-50% patients

Atez	0.78(0.44,1.39)	0.69 (0.32, 1.5)	1.11(0.68,1.82)	~	~	0.59 (0.32, 1.11)
	Atez+Chemo	0.89 (0.45, 1.74)	**1.43(1.05,1.94)**	~	~	0.77 (0.47, 1.25)
		Camre+Chemo*	1.61(0.89,2.93)	~	~	0.86 (0.43, 1.77)
Atez			**Chemo**	~	~	**0.53 (0.36, 0.79)**
1.05 (0.53, 2.13)	**Atez+Chemo**			**Nivo**	~	~
~	~	**Camre+Chemo**			**Pembro**	~
1.04 (0.58, 1.88)	0.99 (0.69, 1.39)	~	**Chemo**			**Pembro+Chemo**
1.11 (0.49, 2.49)	1.05 (0.54, 2)	~	1.06 (0.61, 1.84)	**Nivo***		
1.13 (0.51, 2.5)	1.08 (0.56, 2.01)	~	1.09 (0.63, 1.86)	1.02 (0.47, 2.21)	**Pembro***	
1.72 (0.83, 3.57)	1.64 (0.92, 2.82)	~	**1.66 (1.07, 2.55)**	1.56 (0.77, 3.14)	1.53 (0.77, 3.04)	**Pembro+Chemo**

Network comparision of OS in PD-L1 1-50% patients

Network comparision of PFS in PD-L1<1% patients

Atez+Chemo	1.15(0.43,3.18)	1.51(0.97,2.45)	~	~	1.1(0.45,2.82)	1.13(0.47,2.88)	0.99(0.48, 2.09)
	Carem+Chemo*	1.32 (0.54, 3.2)	~	~	0.96(0.3,3.15)	0.99(0.31,3.25)	0.86 (0.3, 2.47)
		Chemo	~	~	0.73(0.33,1.61)	0.75(0.34,1.65)	0.66(0.37, 1.16)
Atez+Chemo			**Durva**	~	~	~	~
~	**Carem+Chemo**			**Durva+Treme**	~	~	~
0.79 (0.55, 1.12)	~	**Chemo**			**Nivo+Chemo**	1.03(0.47,2.25)	0.9 (0.34, 2.37)
0.67 (0.33, 1.36)	~	0.85 (0.46, 1.58)	**Durva***			**Nivo+Ipi**	0.87 (0.33, 2.3)
1.09 (0.52, 2.24)	~	1.37 (0.72, 2.61)	1.61 (0.86, 3.04)	**Durva+Treme***			**Pembro+Chemo**
1.02 (0.5, 2.03)	~	1.28 (0.7, 2.36)	1.51 (0.63, 3.59)	0.93 (0.39, 2.26)	**Nivo+Chemo**		
1.28 (0.63, 2.52)	~	1.61 (0.88, 2.94)	1.9 (0.8, 4.48)	1.17 (0.49, 2.81)	1.26 (0.69, 2.28)	**Nivo+Ipi**	
1.53 (0.72, 3.14)	~	**1.92 (1, 3.65)**	2.27 (0.92, 5.51)	1.4 (0.56, 3.48)	1.5 (0.61, 3.59)	1.19 (0.49, 2.86)	**Pembro+Chemo**

Network comparision of OS in PD-L1<1% patients

FIGURE 5 League tables of pooled mixed comparison, which show the value of HR/OR with 95% CI between two random treatment agents (all groups were included, for example, "Network comparison of OS in nonselective PD-L1 patients" meant the OS analysis in all patients without PD-L1 section, so as others. * meant that only one survival index was accessed and included: OS or PFS. Durva* and Durva+Treme* were from MYSTIC, a three-arm study; Nivo +Ipi* was from checkmate 227, a three-arm study; Camre+Chemo was from Camel, an ongoing head-to-head study; Pembro* was from Keynote 024 and Keynote 042, both focusing on PD-L1 positive NSCLC)

alone or combination regimens. The patients included in the analysis had advanced/metastatic NSCLC, without *ALK*/*EGFR* mutation. The endpoints were OS and PFS, as well as the incidence rate of any cause high-AEs. Based on 13 well-controlled randomized clinical trials, our results may provide evidence for clinical practice as follows: (1) The addition of PD-1/L1 inhibitors to chemotherapy may provide more survival benefits compared with chemotherapy

Network comparision of PFS in non-squamous patients

Atez	0.78 (0.38, 1.59)	0.78 (0.34, 1.82)	1.3 (0.73, 2.34)	~	1.67 (0.73, 3.9)	~	0.72 (0.3, 1.69)	0.64 (0.31, 1.36)
	Atez+Chemo	1 (0.48, 2.1)	**1.67 (1.11, 2.52)**	~	**2.15 (1.04, 4.45)**	~	0.92 (0.43, 1.96)	0.82 (0.46, 1.53)
		Camre+Chemo	1.66 (0.9, 3.06)	~	2.14 (0.91, 5.03)	~	0.92 (0.38, 2.19)	0.82 (0.39, 1.77)
			Chemo	~	1.29 (0.71, 2.35)	~	0.55 (0.29, 1.03)	**0.49 (0.32, 0.78)**
Atez				**Durva**	~	~	~	~
1.01 (0.54, 1.89)	**Atez+Chemo**				**Nivo**	~	0.43 (0.18, 1.01)	**0.38 (0.18, 0.82)**
1.14 (0.53, 2.41)	1.13 (0.59, 2.15)	**Camre+Chemo**				**Nivo+Ipi**	~	~
0.83 (0.5, 1.4)	0.83 (0.58, 1.17)	0.73 (0.42, 1.27)	**Chemo**				**Pembro**	0.89 (0.42, 1.96)
1.19 (0.56, 2.52)	1.18 (0.61, 2.25)	1.04 (0.48, 2.26)	1.43(0.83,2.46)	**Durva***				**Pembro+Chemo**
0.71 (0.34, 1.48)	0.71 (0.38, 1.31)	0.62 (0.3, 1.33)	0.85 (0.51, 1.43)	0.6 (0.28, 1.27)	**Nivo**	**Nivo+Ipi***		
0.98 (0.48, 2.02)	0.97 (0.52, 1.79)	0.86 (0.41, 1.8)	1.18 (0.71, 1.95)	0.82 (0.4, 1.72)	1.38 (0.67, 2.82)		**Pembro**	
1.44 (0.67, 3.06)	1.43 (0.73, 2.73)	1.26 (0.58, 2.77)	**1.73(1,3.01)**	1.21 (0.55, 2.63)	2.02 (0.94, 4.3)	1.47 (0.69, 3.11)		**Pembro+Chemo**
1.48 (0.77, 2.84)	1.47 (0.86, 2.49)	1.3 (0.66, 2.57)	**1.78(1.2,2.65)**	1.25 (0.64, 2.45)	**2.09 (1.08, 3.99)**	1.52 (0.8, 2.86)	1.03 (0.52, 2.07)	

Network comparision of OS in non-squamous patients

Network comparision of PFS in squamous patients

Atez+Chemo	1.41 (0.38, 5.32)	~	2.58(0.39,17.06)	~	0.49 (0.07, 3.55)	0.81 (0.12, 5.27)
	Chemo	~	1.83 (0.47, 7.08)	~	0.35 (0.08, 1.51)	0.57 (0.15, 2.15)
		Durva	~	~	~	~
			Nivo	~	0.19 (0.03, 1.4)	0.31 (0.05, 2.07)
Atez+Chemo				**Nivo+Ipi**	~	~
0.88 (0.54, 1.44)	**Chemo**				**Pembro**	1.63 (0.23, 11.63)
0.99 (0.45, 2.17)	1.12 (0.6, 2.08)	**Durva***				**Pembro+Chemo**
1.07 (0.5, 2.32)	1.22 (0.67, 2.23)	1.09 (0.46, 2.58)	**Nivo**			
1.28 (0.62, 2.62)	1.45 (0.85, 2.47)	1.29 (0.57, 2.9)	1.19 (0.53, 2.64)	**Nivo+Ipi***		
1.2 (0.48, 3)	1.37 (0.63, 2.96)	1.22 (0.45, 3.28)	1.12 (0.42, 3)	0.94 (0.37, 2.39)	**Pembro**	
1.24 (0.61, 2.5)	1.41 (0.85, 2.32)	1.26 (0.57, 2.76)	1.16 (0.53, 2.52)	0.97 (0.47, 2.01)	1.03 (0.41, 2.59)	**Pembro+Chemo**

Network comparision of OS in squamous patients

Atez										
0.23(0.13,0.41)	**Atez+Chemo**									
0.16(0.08,0.32)	0.67(0.37,1.22)	**Camre+Chemo**								
0.39(0.24,0.63)	**1.65(1.25,2.18)**	**2.46(1.45,4.19)**	**Chemo**							
1.61(0.81,3.21)	**6.8(3.93,12)**	**10.24(4.98,20.9)**	**4.12(2.57,6.77)**	**Durva**						
1.26(0.63,2.53)	**5.35(3.07,9.4)**	**8.0(3.9,16.4)**	**3.52 (2,5.32)**	0.79(0.5,1.23)	**Durva+Treme**					
0.19(0.1,0.37)	0.82(0.48,1.39)	1.22(0.61,2.45)	**0.5(0.32,0.78)**	**0.1（0.06,0.23）**	**0.15（0.08,0.3）**	**Ipi+Chemo**				
1.88(0.92,3.83)	**7.97(4.42,14.43)**	**11.87(5.68,24.92)**	**4.83(2.87,8.17)**	1.1（0.57,2.38）	1.2（0.73,3.04）	**9.7（4.89,19.41）**	**Nivo**			
0.45(0.23,0.85)	**1.89(1.15,3.14)**	**2.82(1.44,5.55)**	1.15(0.76,1.75)	**0.2（0.15,0.53）**	**0.3（0.19,0.67）**	**2.3（1.25,4.31）**	**0.24（0.12,0.46）**	**Nivo+Ipi**		
1.17(0.63,2.07)	**4.96(3.13,7.58)**	**7.4(3.87,13.69)**	**3.01(2.1,4.16)**	0.7（0.39,1.29）	0.93（0.5,1.65）	**6.0（3.38,10.49）**	0.62(0.32,1.14)	**2.62(1.48,4.41)**	**Pembro**	
0.31(0.17,0.55)	1.33(0.85,2.01)	**1.98(1.05,3.65)**	0.81(0.57,1.1)	**0.2（0.11,0.34）**	**0.2（0.14,0.44）**	1.63（0.92,2.78）	**0.17(0.09,0.3)**	0.7(0.4,1.16)	**0.27(0.17,0.43)**	**Pembro+Chemo**

Network comparision of AEs

FIGURE 5 (Continued)

according to OS and PFS. (2) Pembro+Chemo and Atez +Chemo were superior over Chemo and any other included treatment agents in OS and PFS benefit irrespective of PD-L1 level. (3) In consideration of PD-L1 level, Pembro and Atez+Chemo were most likely to improve survival profiles including both OS and PFS in the PD-L1 ≥ 50% cohort. However, in the PD-L1 < 50% cohort, Pembro+Chemo was more likely to exhibit superior survival benefit in terms of both OS and PFS. (4) According to histology, nonsquamous patients were likely to gain more survival benefit than squamous patients by using the advantageous Pembro+Chemo agents. (5) The addition of PD-1/L1 inhibitors to Chemo appeared to increase the toxicity over Chemo alone except Pembro. (6) Pembro+Chemo could balance efficacy and safety well, which ranked first for both OS and PFS for PD-L1 nonselective NSCLC and last for high-AEs across all immunochemo combination strategies.In the last 10 years, the promising results of ICI treatments from randomized clinical exploration for many kinds of tumors have been given extensive attention, including in NSCLC patients. Since 2015, when the second-line ICI agents for NSCLC showed satisfactory results, a series of PD-1/L1 inhibitors, such as pembrolizumab, nivolumab, atezolizumab, have been approved.[30–33] Pembrolizumab was initially approved as a first-line treatment strategy for advanced/metastatic NSCLC patients with high PD-L1 expression level (KN024), then pembrolizumab plus chemotherapy and atezolizumab plus chemotherapy were gradually applied to clinical practice for any PD-L1 expression NCSLC patients under the approval of EMA (European Medicines Agency) and the guidance of ESMO (European Society for Medical Oncology) guidelines.[12] More and more randomized clinical trials focusing on frontline PD-1/L1 treatments for advanced NCSLC are being performed at a rapid pace.

Based on nine randomized clinical trials (RCTs), we found that Pembro+Chemo and Atez+Chemo were superior to Chemo and any other included treatment agents in OS benefit. With a significant difference between Pembro+Chemo and Atez+Chemo, the former agents brought higher benefit than the latter one in OS comparison. As for PFS comparison, three combination strategies including Pembro+Chemo, Carem +Chemo, Atez+Chemo were superior to Chemo alone, and there was no PFS benefit difference among these three regimens. Pembro+Chemo was probably the best regimen to offer both OS and PFS benefit, irrespective of PD-L1 status, and this was in accordance with previous analyses.[12,34]

As for PD-L1 high subgroup analysis, the OS benefit of Pembro, Atez+Chemo were significantly higher than other treatments examined, with no difference between them. As for PFS comparison, there was a better response to Pembro, Atez+Chemo, Pembro+Chemo than the other regimens, which is in line with the previous NMA conclusions.[12,13] There was no significant difference among these three regimens. Hence, Pembro was suggested to be the best treatment strategy to offer both better OS benefit and PFS benefit for PD-L1 > =50% NSCLC patients.

When examining the PD-L1 intermediate subgroup, Pembro+Chemo and Atez+Chemo provided significant PFS benefit compared to Chemo, which were consistent with previous studies. In the PD-L1 negative cohort, pembrolizumab combination agents were indicated to possibly show the best benefit for both OS and PFS. Therefore, Pembro+Chemo was more likely to be the better treatment strategy for PD-L1 < 50% NSCLC.

When it came to subpopulation by histology, again Pembro+Chemo was the better strategy in prolonging OS in nonsquamous NSCLC patients, followed by Pembro alone, and there was no difference between these two agents. Pembro+Chemo also showed more benefit in PFS improvement. In contrast, in terms of squamous patients, all the strategies included were equal and no superior treatment agent was found with regard to OS or PFS. Thus, Pembro +Chemo may be suggested to be the optimal agent for nonsquamous NSCLC.

As for the safety analysis cohort, monoimmunotherapy strategies were less likely to cause high-AEs and be safer than immunochemo combination agents. Notably, most immunochemo combination regimens increased toxicity upon comparison with traditional chemotherapy, but Pembro+Chemo did not increase the risk of causing grade ≥ 3 adverse events compared with Chemo, meaning reliable safety as first-line treatment.

A previous study indicated that PD-L1 level is associated with a different prognosis, in particular that a high PD-L1 level tends to indicate a poor prognosis,[35] but that PD-L1 positive patients are more sensitive to anti-PD1/L1 drugs and thereby obtain greater relief.[36] In accordance with previous studies, our analysis focused on subgroup analysis according to PD-L1 level, which suggests that NSCLC with different PD-L1 expression level should be treated with different treatment agents for better survival benefits, with a notable PD-L1 expression threshold at 50%.

In addition, histological types have also been deemed to be associated with obtaining different clinical therapeutic effects.[36–38] Similar to previous results, we found that nonsquamous NSCLC and squamous NSCLC were suitable for different treatment agents, with Pembro+Atez better for nonsquamous NSCLC and Pembro alone better for squamous NSCLC in our study.

In comparison with previous conclusions,[13] we also found different treatment agents exhibited different efficacy benefits in this study. Several reasons are given from the perspective of signal pathways including PD-1/L1 pathway, PD-1/L2 pathway, PD-L1/B7-1(CD80) pathway and the heterogeneous combination treatment regimens. For example, apart from blocking the binding of PD-1 to PD-L1, PD-1 inhibitors and PD-L1 inhibitors can additionally block different pathways independently, including PD-L1/B7-1 pathway and PD-1/PD-L2 pathways[31,39,40] leading to different clinical effects between anti-PD-1 and anti-PD-L1 drugs. In addition, as previously described,[41] we found that anti-PD-1 drugs were superior than anti-PD-L1 drugs with regard to survival benefit; Pembro+Chemo exhibited higher OS benefit than Atez+Chemo. Furthermore, chemotherapy can aid in enhancing the antigenicity and immunogenicity of malignant cells, resulting in stronger immune attacks by ICIs,[13] which have been shown as better survival benefits when adding PD-1/L1 inhibitors to chemotherapy.

A strength of this NMA was that the search was thorough and included the latest information on RCT. In addition, by assessing the quality of eligible studies, we found that the trials included in our research were relatively well-controlled. Additionally, this NMA provides evidence for the effectiveness and safety between various treatment regimens including monoimmunotherapy, dual-immunotherapy, chemotherapy alone and chemoimmunotherapy, which still lacks sufficient evidential support from clinical trials.

However, we acknowledge that there are several limitations in our analysis. First, the benefit effects of Pembro alone according to OS and PFS were not available in the PD-L1 nonselective cohort due to the design of the original studies included (Keynote 042,[10] Keynote024[18,19]), but the evaluation of pembro monotherapy can be found in other cohorts. Second, our study was based on published results rather than original individual patient data, which may have led to some discount in credibility, but this is an unavoidable problem with a meta-analysis.

In conclusion, subject to the limitations described above, this NMA indicates that the combination of Pembro/Atez and Chemo are preferred first-line treatments for most patients with wild-type NSCLC with regard to efficacy especially for non-squamous NSCLC. Of note, Pembro + Chemo, which exhibited the most reliable safety simultaneously, are most likely to be optimal agents according to both high efficacy and high safety. In addition, this study suggests that PD-L1 status may affect the clinical selection of treatment agents with a threshold at 50%. However, more well-controlled randomized clinical trials are urgently needed in order to further research.

CONFLICT OF INTEREST

There are no conflicts of interest.

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