



Compare the efficacy and safety of programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) inhibitors for advanced non-small cell lung cancer: a Bayesian analysis

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Background: Inhibitors of programmed cell death-1 (PD-1) and its ligand (PD-L1) have represented a novel approach for the management of advanced non-small cell lung cancer (NSCLC). In this study, we aimed to estimate five anti-PD-1/L1 agents (nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab) using network meta-analyses (NMAs) and the Bayesian method to provide suggestions for advanced NSCLC treatments.

Methods: We searched PubMed, Web of Science, Embase, and the Wiley Online Library for eligible studies published up to March 2020. Both pairwise analyses and NMAs were conducted with clinical outcomes, including overall survival (OS), progression-free survival (PFS), objective response rate, and the incidences of adverse events. Results were presented in several patient populations according to treatment lines and PD-L1 status.

Results: Nineteen randomized clinical trials (RCTs) involving 11,456 patients were included in our study. PD-1/L1 inhibitors showed significant benefits over chemotherapies in OS regardless of tumor PD-L1 status [first-line settings: OS =0.85, 95% CI (0.77, 0.94), $I^2=37%$; second- or further-line settings: OS =0.77, 95% CI (0.71, 0.84), $I^2=37%$]. The combined regimen of pembrolizumab and chemotherapy stood out to be the most effective and safest for patients in the first-line settings. Pembrolizumab monotherapy was showed to be the best especially for patients with PD-L1 $\geq 50%$. In the subsequent-line settings, nivolumab ranked the best in improving the survival of patients, and durvalumab had the greatest effect in tumor shrinkage. Atezolizumab, followed by nivolumab, ranked the safest in reducing adverse events, whereas durvalumab was showed with the largest side effects among the five inhibitors.

Conclusions: The combination of pembrolizumab with chemotherapy is suitable for advanced NSCLC patients who have not received any systematic treatments before, and pembrolizumab monotherapy should also be considered, especially for patients with highly-expressed PD-L1 ($\geq 50%$). Nivolumab is the best option for patients with advanced NSCLC whose tumors have progressed following chemotherapies or combined modalities of treatments including chemotherapy. However, our results need to be further validated in future head-to-head clinical trials.

Keywords: Non-small cell lung cancer (NSCLC); checkpoint inhibitors (ICIs); programmed cell death-1 (PD-1); programmed cell death ligand-1 (PD-L1); network meta-analysis (NMA)

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Introduction

Lung cancer has remained the most common cause of cancer death in recent years, and non-small cell lung cancer (NSCLC) represents 87% of all cases, including adenocarcinomas and squamous cell carcinomas as its main subtypes (1-4). For advanced NSCLC patients, molecular targeted therapy is considered to be a standard first-line regimen for those with genomic mutations, while platinum-based doublet chemotherapy optimizes treating efficacy for those with unknown mutational status (5,6). Options such as pemetrexed and docetaxel serve as second-line and beyond or maintenance therapy for advanced NSCLC with poor tumor response or disease progression (7,8). Apart from the treatments above, immunotherapy has been a novel approach for advanced NSCLC over the last decade, where the inhibition of immune checkpoints plays a pivotal role, including programmed cell death-1 (PD-1) and its ligand programmed death ligand-1 (PD-L1) (9,10). Nivolumab and pembrolizumab are PD-1-targeted inhibitors, whereas atezolizumab, durvalumab, as well as avelumab exert their inhibitory potency on PD-L1 (11).

In advanced NSCLC, all of the five above immune checkpoint inhibitors (ICIs) have shown anticancer activity in earlier phase I or II trials, with objective response rates (ORR) varying between 20–40% (12-16). Phase III randomized clinical trials (RCTs) were subsequently conducted to validate the clinical efficacy of these ICIs, given the promising efficacy obtained in the preceding studies. Patients were reported to benefit from PD-1/L1 inhibitors in almost all late-phase trials, regardless of the treatment line (17-21). When compared to chemotherapy, previous meta-analyses combining these RCTs above have also shown promising survival benefits as well as safety profiles for all three approved inhibitors, including nivolumab, pembrolizumab, and atezolizumab (22-25). An indirect analysis has shown therapeutic advantages of PD-1 inhibitors, nivolumab and pembrolizumab, over PD-L1 inhibitor, atezolizumab, in pretreated patients with NSCLC (26), but the evidence is still lacking and there is still a lack of head-to-head comparisons

to directly determine the best agent. In the present study, we performed a systematic review and meta-analysis of several phase II/III RCTs associated with PD-1/L1 inhibitors in advanced NSCLC. The ultimate purpose of this study was to determine the relative efficacy and safety of the existing PD-1/L1 inhibitors in both the first and subsequent settings. The results provided suggestions for clinicians to develop individualized treatments with PD-1/L1 inhibitors for diverse patients with advanced NSCLC. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-192>).

Methods

Protocol and registration

The present report has been prepared according to the recommendations of the Cochrane Comparing Multiple Interventions Methods Group and the PRISMA extension statement for systematic reviews incorporating network meta-analyses (NMAs). The protocol of this study was also registered with PROSPERO (ID: CRD 42020163743) (<https://www.crd.york.ac.uk/prospero/>).

Selection criteria

Studies were considered if they met the inclusion criteria as follows: (I) prospective RCTs; (II) patients with histologically proven diagnosis of advanced NSCLC; (III) studies comparing the addition or single use of PD-1/L1 inhibitors with platinum-based chemotherapy among patients with no prior systemic anticancer therapies in the first-line settings; and studies comparing PD-1/L1 inhibitor monotherapy with chemotherapy among patients whose tumors have progressed or recurred following (adjuvant or neo-adjuvant) combined modalities including chemotherapies in the second- or further-line settings; (IV) studies reporting efficacy outcomes, including overall survival (OS), progression-free survival (PFS), and ORR; and (V) studies displayed with safety profiles, including

the incidence of severe adverse events (SAEs) as well as respiratory and thoracic disorders. Furthermore, the following studies were excluded to minimize the risk of bias: (I) unrandomized studies, retrospective studies, reviews, meta-analysis, case reports, conference reports, letters, or comments; (II) studies in which the comparison drugs were in combination with radiotherapy, other targeted drugs (other than bevacizumab) or other immunotherapy drugs; and (III) studies lacking necessary data or overlapped studies.

Search strategy

We started to search on the PubMed, Web of Science, Embase, and the Wiley Online Library from August 2019 for eligible studies published up to March 2020, with a language restriction of English. The following groups of keywords and medical terms were used: (“non-small cell lung cancer” or “non-small cell lung carcinoma” or “non-small cell lung neoplasms” or “lung adenocarcinoma” or “lung squamous cell carcinoma” or “large cell lung cancer”) and (“programmed death 1” or “PD-1” or “programmed death-ligand 1” or “PD-L1” or “immunotherapy” or “immune checkpoint inhibitors” or “PD-1/PD-L1 inhibitors” or “PD-1/PD-L1 blockades” or “anti-PD-1/PD-L1” or “nivolumab” or “pembrolizumab” or “atezolizumab” or “durvalumab” or “avelumab”). We manually reviewed the reference lists of relevant studies and tracked the “clinicaltrials.gov” site (<https://clinicaltrials.gov/>) for the latest updated data on the eligible studies.

Selection process

A four-phase process was conducted for the selection of studies according to the PRISMA Statement. After searching for records on the websites, studies were screened based on the publication categories specified in the above criteria. Studies were further assessed with full-texts according to their study design and reported outcomes. Eligible ones were finally included if the characteristics of participants, interventions, and outcomes were similar across each study. Two reviewers (Liang and Sui) independently examined publications that met the inclusion criteria. Discrepancies were solved by discussion or adjudication with a third reviewer (Li). Studies were selected with the longest time of follow-up if they had experienced multiple intervals of analysis.

Data extraction

The parameters for efficacy in this study were OS, PFS as well as ORR, and the incidence of SAEs, as well as the respiratory and thoracic disorders, which were used to analyze the safety profiles. Survival outcomes, OS and PFS, were reported with hazard ratios (HRs) together with 95% confidence intervals (CIs). Of note, when HRs could not be extracted from the results in the literature, they would be computed by extractions of survival curves using Engauge Digitizer software with a high degree of accuracy according to established methods (27). Other outcomes, ORRs and the incidence of adverse events, were extracted or calculated using the original number of reporting events following established methods (28). General characteristics of outcomes and enrolled patients in the included studies were obtained.

Assessment of risk of bias

The qualities of included trials were assessed following the instructions of the Cochrane Handbook for Systemic Reviews of Interventions, in which six aspects were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (29). Effect account was estimated through sensitive analyses for the impact of included studies with high or unclear risk of bias.

Statistical analysis

Data were first analyzed through direct pairwise comparisons in all intention-treated patient population, and the results presented with pooled-estimated HRs (HR_{pooled}) together with 95% CIs. Mixed treatment comparisons incorporating direct and indirect results were subsequently generated within Bayesian frameworks using Markov chain Monte Carlo methods. Analyses above were performed by Review Manager (version 5.3) (<https://community.cochrane.org/help/tools-and-software/revman-5>) and R (version 3.6.1) as well as R packages (<https://www.r-project.org/>). In the R package ‘gemtc’, each chain was fitted with 20,000 iterations. Afterward, different regimens were ranked by efficacy and safety outcomes by calculating the hazard ratios (HRs) or relative risks (RRs) as well as the proportion of iterations of the Markov chain. Ranking probabilities of

treatments were estimated to determine the likelihood of therapies in a best-to-worst order.

Heterogeneity between studies was measured by the I-square test and P value. If the I-square value was $\geq 75\%$, we would regard it as high heterogeneity, and $< 25\%$, as low heterogeneity, while others would remain as medium heterogeneity. The random effect-based model by Der Simonian and Laird was used to perform meta-analyses for studies with high heterogeneity, while the fixed effect-based Mantel-Haenszel model was used for the low and medium heterogeneous models (30,31). All the results were considered to be of significance with a value of $P < 0.05$, and no significance was attributed otherwise. Sensitivity analyses were conducted in case of high heterogeneity ($\geq 75\%$), and studies which would largely affected the heterogeneity were omitted from the model one after another based on the sensitivity results. Before and after the omissions, pooled efficacy and safety together with the statistical significances were compared.

Ethical statements

Ethical approval was exempted by the Institutional Review Committee of Zhongshan Hospital, Fudan University, Shanghai, China.

Results

Literature search results

The literature search identified a total of 249 records, of which 34 were excluded because of duplicates; 127 records were excluded because of reviews, case reports, conference reports, letters, comments or summaries; three records were excluded because of meta-analyses; 28 records were excluded because of non-perspective RCTs; seven records were excluded because of early phases; 10 records were excluded because of the same trial with multiple follow-ups; three records were excluded because the combination of PD-1/L1 inhibitors or chemotherapy was combined with other drugs or therapies (other than bevacizumab); four records were excluded because of mixed diagnosis of patients enrolled; and three records were excluded because of insufficient result posted. A total of 28 trials were assessed as eligible ones and nine studies were excluded because of their heterogeneity and incompatibility for the quantitative analysis.

Finally, 19 studies involving 11,456 participants with advanced NSCLC (eleven studies with PD-1/L1 inhibitors

in the first-line settings involving 6,635 patients and eight studies with PD-1/L1 inhibitors in the subsequent settings involving 4,821 patients) met all the inclusion or exclusion criteria and were included in the meta-analysis (17,19,20,32-44). All of the five anti-PD-1/L1 agents were covered in our study. In the included studies, patients were originally stratified into subgroups by the expressing PD-L1 status of tumor cells, which was presented by the tumor proportion score (TPS). The cutting-off points of PD-L1 TPS included 1%, 5%, 10%, 25%, and 50%. 1% and 50% were finally selected as cut-offs for our subgroup meta-analyses because they were the most intersections for the clinical results reported by different studies that we had included. A PRISMA diagram summarizing our literature search results and selection is shown in *Figure 1*. The general characteristics of enrolled patients in the included trials, as well as clinical outcomes, are outlined in *Tables 1,2*. The whole network is illustrated in *Figure 2*, in which solid lines between the different drugs represent the number of studies, and dashed lines represent indirect comparisons that we can obtain through the network.

Assessment of risk of bias

Seventeen of all were considered at high risk of bias in performance and detection because they were open-label. Although only two of these studies (Keynote 189 & Keynote 407) were double-blind, outcomes on whether patients could benefit from PD-1/L1 inhibitors or not were reported to be similar to those in open-label trials. Nine undergoing studies were at a high risk of attrition bias resulting from the incomplete outcomes. Data on risk of bias of each included study are presented in *Figure S1A*. Results of any assessment of risk of bias across studies are illustrated in *Figure S1B*.

Comparisons of regimens

Drug efficacy

First-line settings

We analyzed three populations of patients in this setting: intention-to-treat (ITT) population as well as patients with PD-L1 TPS $\geq 1\%$ and TPS $\geq 50\%$. Sensitivity analyses were performed in the following models with high heterogeneity, and none of the pooled results showed any alteration in the statistical significance after the heterogeneity reduction. According to results of pair-wise comparisons, additions of PD-1/L1 inhibitors to chemotherapy were shown to be

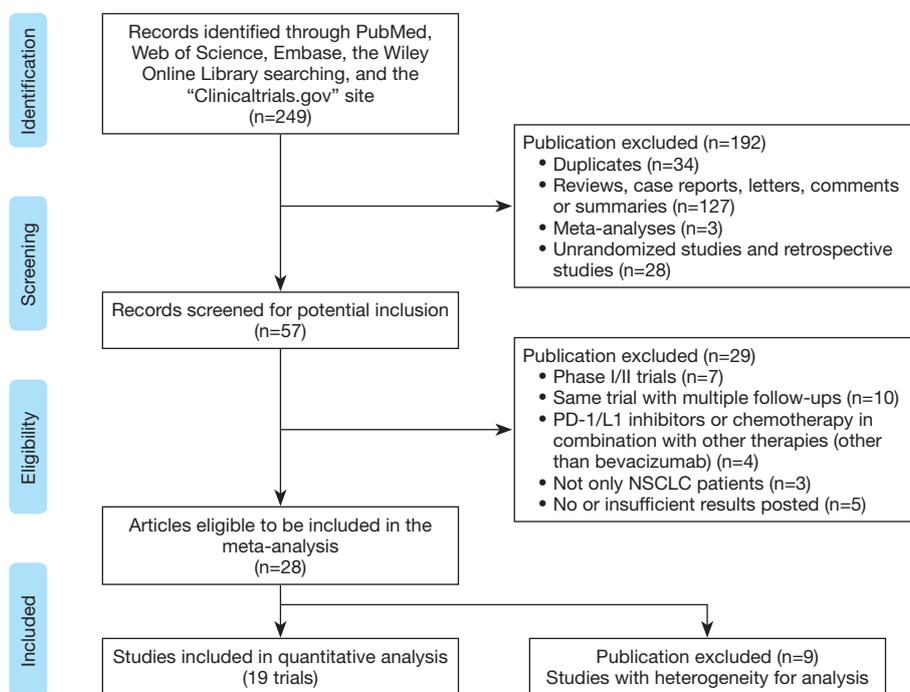


Figure 1 PRISMA diagram of search results and selections.

superior to chemotherapeutic drugs alone in terms of OS [OS HR_{pooled} = 0.85; 95% CI (0.77, 0.94); I² = 37%] and PFS [PFS HR_{pooled} = 0.63; 95% CI (0.58, 0.69); I² = 58%] (Figure S2A,B). Benefits were also significant in terms of ORR [ORR RR_{pooled} = 1.30; 95% CI (1.17, 1.46); I² = 71%] (Figure S2C). In the population of patients with PD-L1 TPS ≥ 1%, both the single use of the PD-1/L1 inhibitors and their combination with chemotherapy showed a significantly lower risk of death for patients, compared with chemotherapeutic drugs [OS HR_{pooled} = 0.84; 95% CI (0.76, 0.92); I² = 49%] (Figure S2D). However, no benefit was shown in terms of PFS in this subgroup of patients [PFS HR_{pooled} = 1.08; 95% CI (0.98, 1.18); I² = 0%] (Figure S2E). Similar results were also reported among patients treated with nivolumab or pembrolizumab monotherapy with PD-L1 TPS ≥ 50% [OS HR_{pooled} = 0.70; 95% CI (0.60, 0.81); I² = 0%; PFS HR_{pooled} = 0.87; 95% CI (0.75, 1.02); I² = 0%] (Figure S2F,G).

According to the ranking results from NMA, the top three of all regimens in terms of efficacy were pembrolizumab combined with chemotherapy, atezolizumab combined with chemotherapy, and pembrolizumab monotherapy. Pembrolizumab combined therapy seemed to be the most effective with a probability of 84% ranking first in OS and 90% in PFS or ORR (Figures 3A,B,S3A) in

the ITT patient population. Its superiority to atezolizumab combined therapy was significant both in OS and PFS [OS HR_{indirect} = 0.69; 95% CI (0.54, 0.86); I² = 14%; PFS HR_{indirect} = 0.77; 95% CI (0.64, 0.93); I² = 0%] (Table 3). It also ranked as the best among the patient with PD-L1 TPS ≥ 1%, with a probability of 58% in OS and a probability of 78% in PFS (Figure 3C,D). The superiority of pembrolizumab combined therapy to pembrolizumab was also both significant in OS and PFS [OS HR_{indirect} = 0.71; 95% CI (0.56, 0.90); I² = 11%; PFS HR_{indirect} = 0.45; 95% CI (0.36, 0.56); I² = 9%] (Table 3).

The combination of atezolizumab and chemotherapy ranked in the second place in both of the ITT population and among patients with PD-L1 TPS ≥ 1%, but there was no significant difference between it and the third-rank pembrolizumab monotherapy, either in terms of PFS or OS. Also, the advantage of pembrolizumab monotherapy was of no significance when compared to the drugs that ranked behind (nivolumab and durvalumab) (Table 3). However, pembrolizumab monotherapy appeared to be the most effective agent with a high probability of 87% in terms of OS and 81% of PFS (Figure S3B,C) for patients with PD-L1 TPS ≥ 50% temporarily, because the lack of efficacy outcomes related to pembrolizumab or atezolizumab combined therapies. The superiority of pembrolizumab to

Table 1 Characteristics of included studies

Study/reference	Trial phase	Sample size	NSCLC patient cohort			Experimental arm (n)	Control arm (n)	Primary/secondary end points	Analysis timing	
			Histology (% SQ)	Stages	Median age (95% CI)					PD-L1 expression
CheckMate026 (32)	III	541	All (24.0)	IV	63.1 (62.3–63.9)	≥1%	Nivolumab (3 mg/kg Q2W) (n=271)	Chemotherapy (n=270)	OS/PFS (PD-L1 ≥1%) OS/PFS (PD-L1 ≥50%)	OS/PFS: final OS/PFS: final
Keynote024 (33)	III	305	All (18.4)	IV	64.2 (63.1–65.3)	≥50%	Pembrolizumab (200 mg Q3W) (n=154)	Chemotherapy (n=151)	PFS/OS (PD-L1 ≥50%)	OS/PFS: final
Keynote042 (17)	III	1,274	All (38.6)	Advanced	62.8 (62.2–63.3)	≥1%	Pembrolizumab (200 mg Q3W) (n=637)	Chemotherapy (n=637)	OS/PFS (PD-L1 ≥1%) OS/PFS (PD-L1 ≥50%)	OS/PFS: interim OS/PFS: interim
Keynote042-China extension	III	262	All (56.1)	Advanced	60.9/61.5 (NA)	≥1%	Pembrolizumab (200 mg Q3W) (n=637)	Chemotherapy (n=637)	OS/PFS (PD-L1 ≥1%) OS/PFS (PD-L1 ≥50%)	OS/PFS: interim OS/PFS: interim
MYSTIC	III	746	NA	IV	63.2/63.6 (NA)	All	Durvalumab (20 mg/kg Q4W) (n=374)	Chemotherapy (n=372)	OS/PFS (ITT) OS/PFS (PD-L1 ≥1%)	OS/PFS: interim OS/PFS: interim
Keynote021 (42)	II	123	Non-SQ (0)	IIIB/IV	63.2/62.2 (NA)	All	Pembrolizumab (200 mg Q3W) + chemotherapy (n=60)	Placebo + chemotherapy (n=63)	OS/PFS (ITT)	OS/PFS: interim OS/PFS: interim
Keynote189 (19)	III	616	Non-SQ (0)	IV	64.5 (62.4–63.8)	All	Pembrolizumab (200 mg Q3W) + chemotherapy (n=410)	Placebo + Chemotherapy (n=206)	OS/PFS (ITT) OS/PFS (PD-L1 ≥1%)	OS/PFS: interim OS/PFS: interim
Keynote407 (20)	III	559	SQ (100.0)	IV	64.9 (64.2–65.6)	All	Pembrolizumab (200 mg) + chemotherapy (n=278)	Placebo + Chemotherapy (n=281)	OS&PFS (ITT) OS&PFS (PD-L1 ≥1%)	OS/PFS: interim OS/PFS: interim
Impower130 (34)	III	724	Non-SQ (0)	IV	64.0 (63.3–64.7)	All	Atezolizumab (1,200 mg Q3W) + chemotherapy (n=483)	Chemotherapy (n=240)	OS&PFS (ITT) OS&PFS (PD-L1 ≥1%)	OS/PFS: final OS/PFS: final
Impower131†	III	683	SQ (100.0)	IV	64.6 (64.1–65.1)	All	Atezolizumab (1,200 mg Q3W) + chemotherapy (n=343)	Chemotherapy (n=340)	OS&PFS (ITT) OS&PFS (PD-L1 ≥1%)	OS/PFS: interim OS/PFS: interim
Impower150 (43)	III	802	Non-SQ (0)	IV	63.0 (NA)	All	Atezolizumab (1,200 mg Q3W) + chemotherapy (n=402)	Bevacizumab (15 mg/kg Q3W) + chemotherapy (n=400)	OS (ITT) OS&PFS (PD-L1 ≥50%)	OS/PFS: interim OS/PFS: interim
CheckMate 017 (21)	III	272	SQ (100.0)	IIIB/IV	63.3 (62.3–64.3)	All	Nivolumab (3 mg/kg Q2W) (n=135)	Chemotherapy (n=137)	OS/PFS (ITT) OS/PFS (PD-L1 ≥1%)	OS/PFS: final OS/PFS: final
CheckMate 057 (36)	III	582	Non-SQ (0)	IIIB/IV	61.6 (60.8–62.4)	All	Nivolumab (3 mg/kg Q2W) (n=292)	Chemotherapy (n=290)	OS/PFS (ITT) OS/PFS (PD-L1 ≥1%)	OS/PFS: final OS/PFS: final
CheckMate 078 (37)	III	504	All (39.7)	IIIB/IV	59.1 (58.3–59.9)	All	Nivolumab (3 mg/kg Q2W) (n=338)	Chemotherapy (n=166)	OS/PFS (ITT)	OS/PFS: final OS/PFS: final
POPULAR (38)	II	287	All (33.8)	IIIB/IV	61.6 (60.5–62.7)	All	Atezolizumab (1,200 mg Q3W) (n=144)	Chemotherapy (n=143)	OS/PFS (ITT) OS/PFS (PD-L1 ≥1%)	OS/PFS: final OS/PFS: final

Table 1 (continued)

Table 1 (continued)

Study/reference	Trial phase	NSCLC patient cohort				Experimental arm (n)	Control arm (n)	Primary/secondary end points	Analysis timing	
		Sample size	Histology (% SQ)	Stages	Median age (95% CI)					PD-L1 expression
OAK (39)	III	1,225	All (26.2)	IIIB/IV	62.8 (62.3–63.3)	All	Atezolizumab (1,200 mg Q3W) (n=613)	Chemotherapy (n=612)	OS/PFS (ITT)	OS/PFS: final
Keynote010 (40)	III	1,033	All (21.5)	Advanced	62.0 (61.4–62.6)	≥1%	Pembrolizumab (2 mg/kg Q3W n=345; 10 mg/kg Q3W n=346)	Chemotherapy (n=343)	OS/PFS (PD-L1 ≥1%)	OS/PFS: final
JAVELIN Lung 200 (41)	III	792	All (30.6)	IIIB–IV	62.7 (62.0–63.4)	All	Avelumab (10 mg/kg Q2W) (n=396)	Chemotherapy (n=396)	OS/PFS (PD-L1 ≥1%)	OS/PFS: final
ARCTIC (44)	III	126	All (25.4)	IIIB–IV	62.7 (NA)	≥1%	Durvalumab (10 mg/kg Q2W) (n=62)	Chemotherapy (n=64)	OS/PFS (PD-L1 ≥1%)	OS/PFS: interim

†, data without published articles. SQ, squamous cell carcinoma; Non-SQ, non-squamous cell carcinoma; OS, overall survival; PFS, progression-free survival.

Table 2 Clinical outcomes in the included studies

Study/reference	Arms	Efficacy				Safety		
		OS: HR (95% CI)		PFS: HR (95% CI)		SAEs (n)	Respiratory/thoracic disorders n.	
		ITT population	Subgroups	ITT population	Subgroups			
CheckMate026 (32)	Nivolumab	-	PD-L1 ≥1%: 1.07 (0.86–1.33); PD-L1 ≥50%: 0.90 (0.63–1.29)	-	PD-L1 ≥1%: 1.17 (0.95–1.43); PD-L1 ≥50%: 1.07 (0.77–1.49)	22/211	155/267	39/267
Keynote024 (33)	Pembrolizumab	-	PD-L1 ≥50%: 0.63 (0.47–0.86)*	-	PD-L1 ≥50%: 0.50 (0.37–0.68)*	69/154	68/154	26/154
Keynote042 (17)†	Chemotherapy	-	PD-L1 ≥1%: 0.81 (0.71–0.93)*; PD-L1 ≥50%: 0.69 (0.56–0.85)*	-	PD-L1 ≥1%: 1.07 (0.94–1.21); PD-L1 ≥50%: 0.82 (0.68–0.99)*	174/637	259/636	102/636
Keynote042-China extension†	Pembrolizumab	-	PD-L1 ≥1%: 0.65 (0.45–0.94)*; PD-L1 ≥50%: 0.62 (0.38–1.00)	-	PD-L1 ≥1%: 1.00 (0.74–1.35); PD-L1 ≥50%: 0.85 (0.57–1.28)	42/138	38/128	12/128
MYSTIC‡	Durvalumab	0.96 (0.81–1.13)	PD-L1 ≥1%: 0.88 (0.73–1.07)	1.24 (1.04–1.48)	PD-L1 ≥1%: 1.09 (0.89–1.34)	88/374	131/369	38/369
Keynote021 (42)	Pembrolizumab + chemotherapy	0.90 (0.42–1.91)	-	0.53 (0.31–0.91)*	-	112/372	112/352	21/352
Keynote189 (19)†	Pembrolizumab + chemotherapy	0.49 (0.38–0.64)*	PD-L1 ≥1%: 0.47 (0.34–0.66)*	0.52 (0.43–0.64)*	PD-L1 ≥1%: 0.44 (0.34–0.57)*	33/60	27/59	8/59
	Chemotherapy					18/63	18/62	3/62
						195/410	202/405	42/405
						39/206	95/202	28/202

Table 2 (continued)

Table 2 (continued)

Study/reference	Arms	Efficacy						Safety		
		OS: HR (95% CI)			PFS: HR (95% CI)			ORR (n)	SAEs (n)	Respiratory/ thoracic disorders n.
		ITT population	Subgroups	ITT population	ITT population	Subgroups				
Keynote407 (20)	Pembrolizumab + chemotherapy	0.64 (0.49–0.85)*	PD-L1 ≥1%: 0.65 (0.45–0.92)*	0.56 (0.45–0.70)*	PD-L1 ≥1%: 0.49 (0.38–0.65)*	161/278	113/278	33/278		
	Chemotherapy					108/281	107/280	27/280		
Impower130 (34)	Atezolizumab + chemotherapy	0.79 (0.64–0.98)*	PD-L1 ≥1%: 0.70 (0.45–1.08)	0.64 (0.54–0.77)*	PD-L1 ≥1%: 0.61 (0.43–0.85)*	–	240/473	73/473		
	Chemotherapy						88/232	21/232		
Impower131†	Atezolizumab + chemotherapy	0.88 (0.73–1.05)	–	0.75 (0.64–0.88)*	–	–	143/334	43/334		
	Chemotherapy						96/334	23/334		
Impower150 (43)	Atezolizumab + chemotherapy	0.85 (0.71–1.03)	–	0.91 (0.78–1.06)	PD-L1 ≥50%: 0.63 (0.43–0.92)*	163/401	230/400	–		
	Bevacizumab + chemotherapy					158/393	231/294	–		
CheckMate017 (21)†	Nivolumab	0.59 (0.43–0.81)*	PD-L1 ≥1%: 0.69 (0.45–1.10)	0.62 (0.47–0.81)*	PD-L1 ≥1%: 0.67 (0.44–1.00)	27/135	61/131	13/131		
	Chemotherapy					12/137	70/129	18/129		
CheckMate057 (36)	Nivolumab	0.73 (0.59–0.89)*	PD-L1 ≥1%: 0.59 (0.43–0.82)*	0.92 (0.77–1.11)	PD-L1 ≥1%: 0.70 (0.53–0.94)*	56/292	134/287	49/287		
	Chemotherapy					36/290	111/268	24/268		
CheckMate078 (37)†	Nivolumab	0.68 (0.52–0.90)*	PD-L1 ≥1%: 0.62 (0.45–0.87)*	0.77 (0.62–0.95)*	–	56/338	131/337	228/337		
	Chemotherapy					7/166	47/156	111/156		
POPLAR (38)†	Atezolizumab	0.69 (0.52–0.92)*	–	0.92 (0.71–1.20)	–	21/144	127/142	21/142		
	Chemotherapy					21/143	125/135	13/135		
OAK (39)	Atezolizumab	0.80 (0.70–0.92)*	PD-L1 ≥1%: 0.64 (0.49–0.84)*	0.96 (0.85–1.08)	–	84/613	194/609	70/609		
	Chemotherapy					72/612	181/578	37/578		
Keynote010 (40)†	Pembrolizumab (2 mg/kg)	–	PD-L1 ≥1%: 0.71 (0.58–0.88)*; PD-L1 ≥1%: 0.61 (0.49–0.75)*	–	PD-L1 ≥1%: 0.88 (0.73–1.04); PD-L1 ≥1%: 0.79 (0.66–0.94)*	62/344	115/339	40/339		
	Pembrolizumab (10 mg/kg)					64/346	131/343	37/343		
	Chemotherapy					32/343	107/309	28/309		
JAVELIN Lung 200 (41)†	Avelumab	0.90 (0.76–1.07)	PD-L1 ≥1%: 0.90 (0.73–1.11)	1.17 (0.98–1.41)	PD-L1 ≥1%: 1.01 (0.80–1.27)	50/264	163/393	55/393		
	Chemotherapy					31/265	143/365	37/365		
ARCTIC (44)	Durvalumab	–	PD-L1 ≥1%: 0.63 (0.42–0.93)*	–	PD-L1 ≥1%: 0.71 (0.49–1.04)	22/62	23/62	11/62		
	Chemotherapy					8/64	16/63	2/63		

*, †, ‡ indicates a statistical significance; †, ‡ studies also with references to the latest online data on the “clinicalgov” site; †, ‡ data without any published articles. ITT population, intention-to-treat population; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; SAEs, severe adverse events; HR, hazard ratio; RR, relative risk.

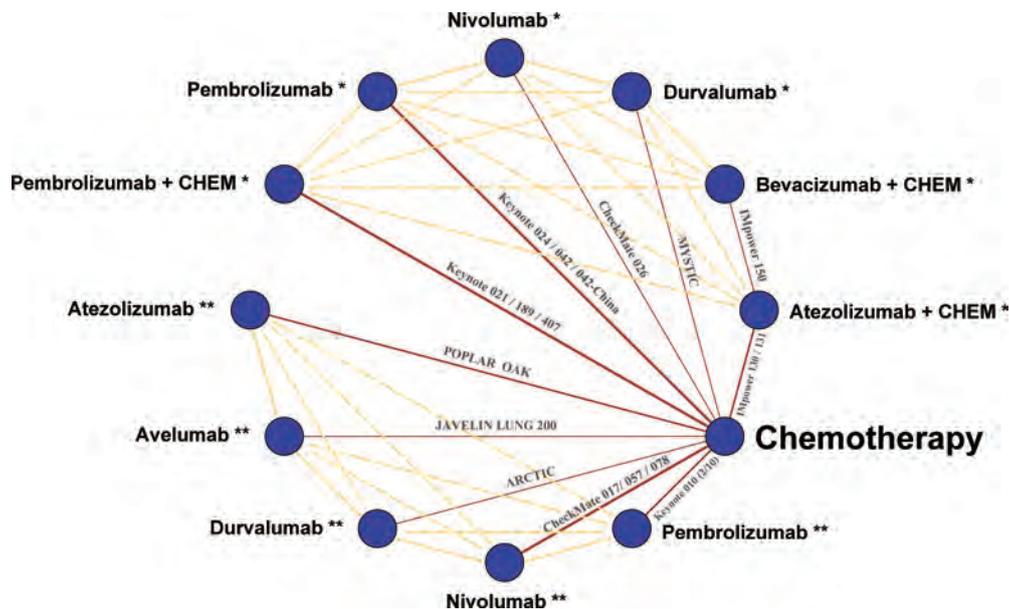


Figure 2 Network graph of trials assessing PD-1/L1 inhibitors in advanced NSCLC. *, in the first-line settings; **, in the second- or further-line settings. NSCLC, non-small cell lung cancer.

nivolumab was also of no significance either in OS or PFS (Table 3). Of note, heterogeneities between studies in the above NMAs were measured to be low or medium in terms of the I^2 test.

In brief, the efficacy of the monotherapy supposed to be inferior to that of the combination therapy in the first-line settings according to the above results. For one thing, neither of durvalumab nor nivolumab monotherapy should be advised to patients because they even appeared to be weaker than chemotherapy when inhibiting the growth of tumors. For another, although it was relatively better than the durvalumab and nivolumab, pembrolizumab monotherapy was still not as effective as the combination therapy of pembrolizumab or atezolizumab, especially for patients harboring tumors that express a low or moderate status of PD-L1. However, these results are still needed to be further validated in future clinical trials.

Second- or further-line settings

Two populations, ITT as well as patients with PD-L1 TPS $\geq 1\%$, were analyzed in these settings. Pooled analyses in the ITT patient population showed a significantly lower risk of death of PD-1/L1 inhibitors when compared to chemotherapy in OS [OS HR_{pooled} = 0.77; 95% CI (0.71, 0.84); $I^2=37\%$] (Figure S4A). However, they showed no significance in reducing the risks of progression among pretreated patients in terms of PFS [PFS HR_{pooled} = 0.92; 95% CI (0.85,

1.00); $I^2=0\%$] (Figure S4B) but showed significantly better ORRs indicated by the pooled RR [ORR RR_{pooled} = 1.67; 95% CI (1.44, 1.93); $I^2=56\%$] (Figure S4C). Subgroups analyses among patients with PD-L1 TPS $\geq 1\%$ showed similar results in OS [OS HR_{pooled} = 0.69; 95% CI (0.63, 0.77); $I^2=35\%$] (Figure S4D) and also PFS [PFS HR_{pooled} = 0.82, 95% CI (0.75, 0.91), $I^2=21\%$] (Figure S4E). Here, sensitivity analyses were conducted on PFS in the ITT population and OS among patients with PD-L1 TPS $\geq 1\%$. Through omitting CheckMate017, a study with a relatively smaller sample size than the other studies of nivolumab and chemotherapy, the significance of advantage of anti-PD-1/L1 drugs in inhibiting tumor progression when compared with chemotherapy changed. The extent of benefits in OS that patients with PD-L1 TPS $\geq 1\%$ could obtain from anti-PD-1/L1 drugs increased after the study related to durvalumab, ARCTIC, was excluded from the pooled analysis.

According to the ranking results from NMA, the top three regimens in terms of efficacy were nivolumab, atezolizumab, and avelumab in the ITT population. Nivolumab ranked as the best option for pretreated NSCLC patients, with probabilities of 77% in OS and 83% in PFS (Figure 4A,B). Its superiority to atezolizumab, the second-place inhibitor was significant both in PFS and ORR, but not in OS [PFS HR_{indirect} = 0.84; 95% CI (0.71, 0.99); $I^2=21\%$; ORR RR_{indirect} = 1.73; 95% CI (1.16, 2.58);

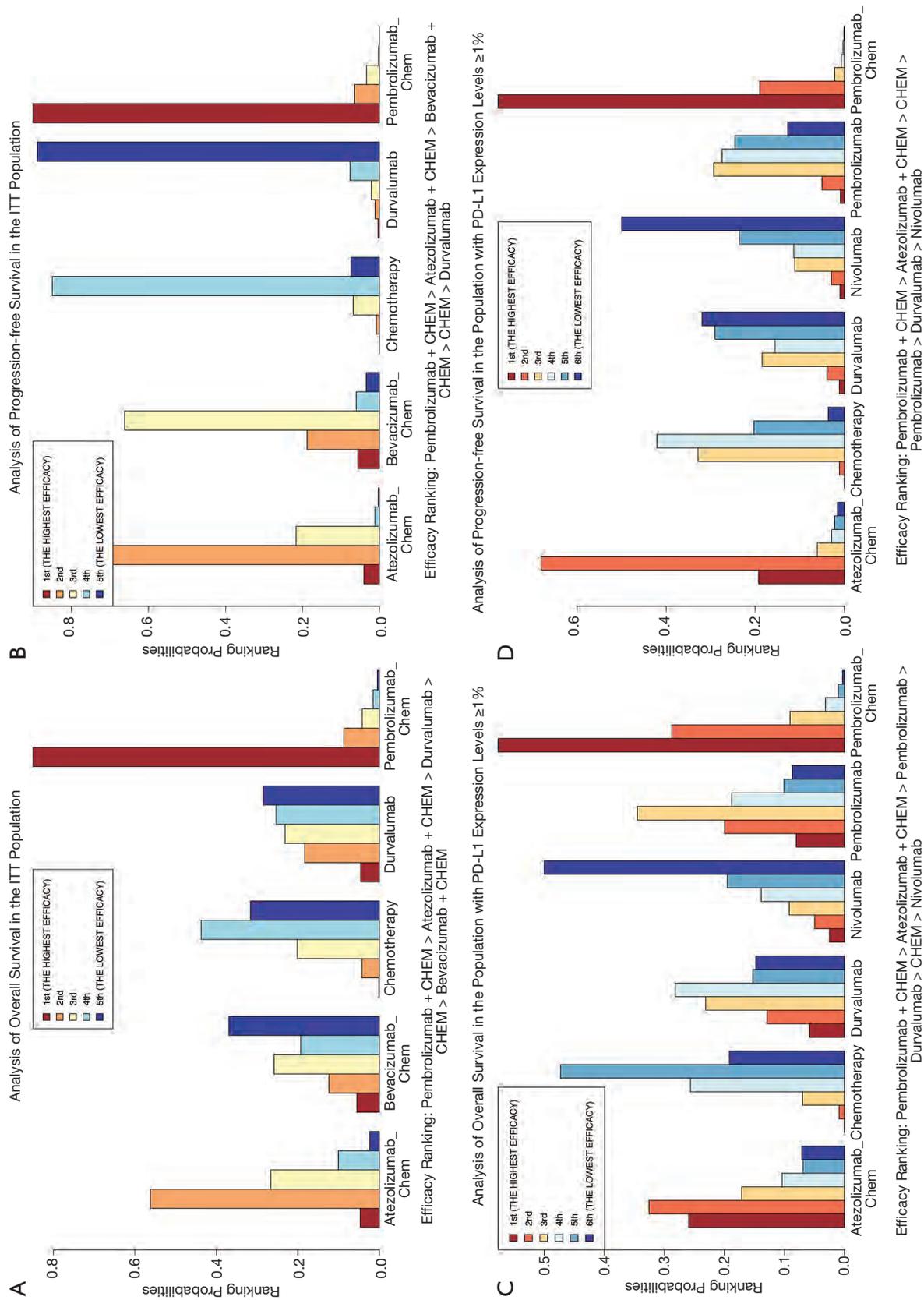


Figure 3 Rankograms of efficacy analyses with PD-1/L1 inhibitors in the first-line settings. (A) Overall survival (OS) in the intention-to-treat (ITT) patient population; (B) progression-free survival (PFS) in the ITT patient population; (C) OS in the patient population with tumor proportion score (TPS) of PD-L1 $\geq 1\%$; (D) PFS in the patient population with PD-L1 TPS $\geq 1\%$.

Table 3 Results of indirect comparisons in the first-line settings

Regimens	OS: HR (95% CI)		PFS: HR (95% CI)		ORR: RR (95% CI)	SAE: RR (95% CI)	Respiratory/thoracic disorders: RR (95% CI)
	ITT population	Subgroups (TPS)	ITT population	Subgroups (TPS)	ITT population		
Pembrolizumab-chemotherapy vs. Atezolizumab-chemotherapy	0.69 (0.54, 0.86)*	≥1%: 0.83 (0.51, 1.34)	0.77 (0.64, 0.93)*	≥1%: 0.77 (0.52, 1.14)	–	0.78 (0.64, 0.94)*	0.56 (0.36, 0.89)*
Pembrolizumab-chemotherapy vs. Pembrolizumab	–	≥1%: 0.71 (0.56, 0.90)*	–	≥1%: 0.45 (0.36, 0.56)*	1.46 (1.09, 1.96)*	0.91 (0.76, 1.09)	0.47 (0.31, 0.72)*
Pembrolizumab-chemotherapy vs. Durvalumab	0.60 (0.47, 0.77)*	≥1%: 0.65 (0.49, 0.87)*	0.44 (0.35, 0.54)*	≥1%: 0.43 (0.32, 0.56)*	2.19 (1.61, 2.97)*	0.98 (0.77, 1.25)	0.58 (0.34, 1.06)
Pembrolizumab-chemotherapy vs. Nivolumab	–	≥1%: 0.54 (0.40, 0.72)*	–	≥1%: 0.40 (0.30, 0.53)*	5.22 (3.93, 6.92)*	0.82 (0.66, 1.02)	0.60 (0.34, 1.07)
Pembrolizumab-chemotherapy vs. Bevacizumab-chemotherapy	0.59 (0.44, 0.79)*	–	0.70 (0.55, 0.89)*	–	–	0.76 (0.61, 0.95)*	–
Atezolizumab-chemotherapy vs. Pembrolizumab	–	≥1%: 0.86 (0.54, 1.36)	–	≥1%: 0.58 (0.40, 0.83)*	–	1.17 (0.97, 1.41)	0.83 (0.54, 1.29)
Atezolizumab-chemotherapy vs. Durvalumab	0.88 (0.71, 1.09)	≥1%: 0.79 (0.49, 1.28)	0.62 (0.48, 0.81)*	≥1%: 0.55 (0.37, 0.82)*	–	1.26 (0.98, 1.16)	1.03 (0.56, 1.90)
Atezolizumab-chemotherapy vs. Nivolumab	–	≥1%: 0.65 (0.40, 1.06)	–	≥1%: 0.52 (0.35, 0.77)*	–	1.05 (0.85, 1.32)	1.07 (0.59, 1.92)
Atezolizumab-chemotherapy vs. Bevacizumab-chemotherapy	0.86 (0.71, 1.03)	–	0.91 (0.78, 1.06)	–	–	0.98 (0.87, 1.10)	–
Pembrolizumab vs. Durvalumab	–	≥1%: 0.92 (0.73, 1.17)	–	≥1%: 0.96 (0.76, 1.21)	1.50 (1.17, 1.91)*	1.07 (0.85, 1.36)	1.24 (0.69, 2.23)
Pembrolizumab vs. Nivolumab	–	≥1%: 0.76 (0.59, 0.98)*; ≥50%: 0.74 (0.50, 1.09)	–	≥1%: 0.90 (0.71, 1.14); ≥50%: 0.66 (0.33, 1.30)	3.57 (2.88, 4.43)*	0.90 (0.73, 1.11)	1.28 (0.73, 2.25)
Pembrolizumab vs. Bevacizumab-chemotherapy	–	–	–	–	–	0.84 (0.67, 1.04)	–
Durvalumab vs. Nivolumab	–	≥1%: 0.82 (0.61, 1.10)	–	≥1%: 0.94 (0.70, 1.25)	2.38 (1.90, 2.99)*	0.84 (0.64, 1.10)	1.03 (0.51, 2.10)
Durvalumab vs. Bevacizumab-chemotherapy	0.98 (0.73, 1.30)	–	1.61 (1.24, 2.08)	–	–	0.78 (0.59, 1.02)	–
Nivolumab vs. Bevacizumab-chemotherapy	–	–	–	–	–	0.93 (0.72, 1.19)	–

* indicates a statistical significance in each indirect comparison. ITT population, intention-to-treat population; TPS, tumor proportion score; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; SAEs, severe adverse events; HR, hazard ratio; RR, relative risk.

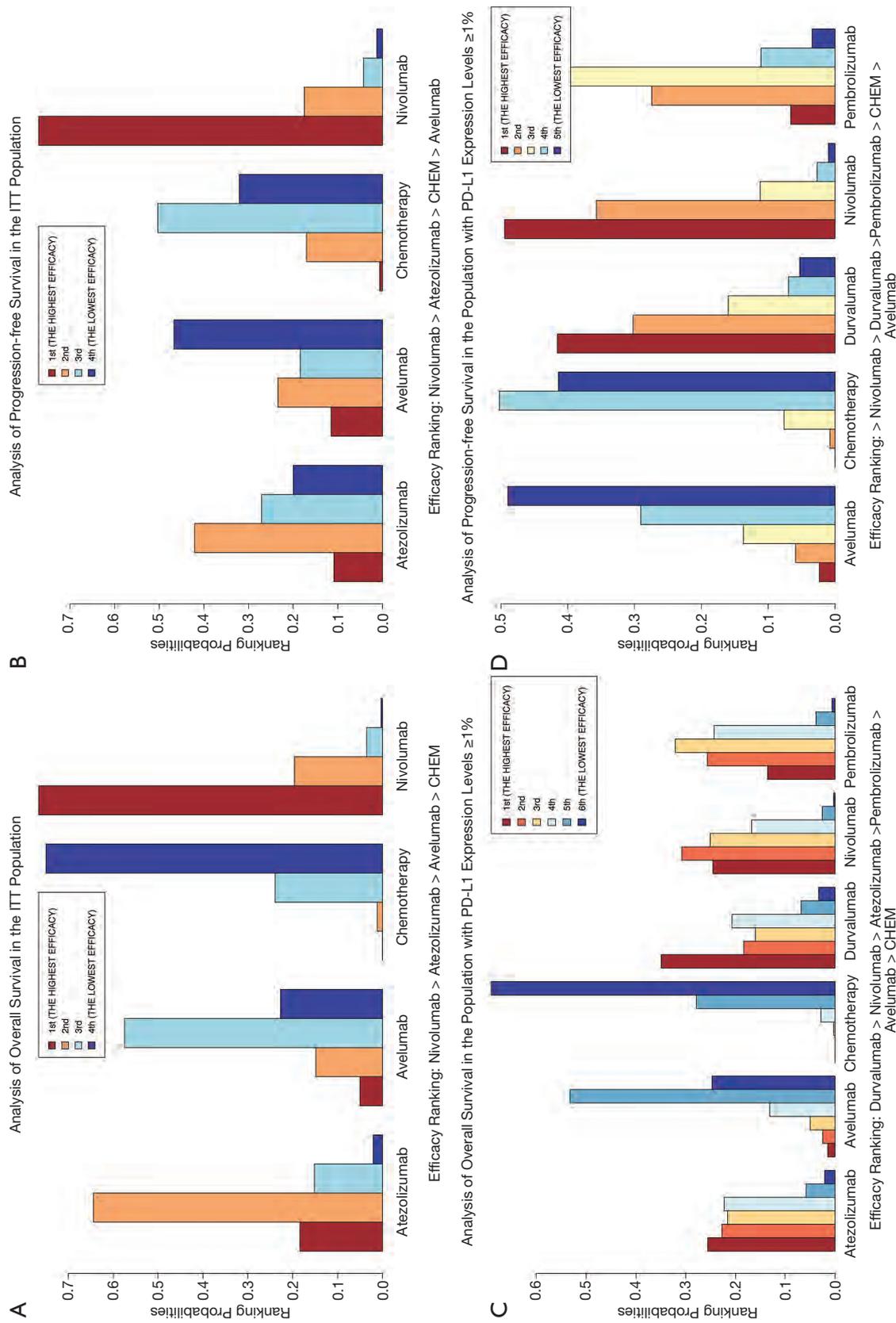


Figure 4 Rankgrams of efficacy analyses with PD-1/L1 inhibitors in the second-or further-line settings. (A) Overall survival (OS) in the intention-to-treat (ITT) patient population; (B) progression-free survival (PFS) in the ITT patient population; (C) OS in the patient population with tumor proportion score (TPS) of PD-L1 $\geq 1\%$; (D) PFS in the patient population with PD-L1 TPS $\geq 1\%$.

$I^2=15\%$]. However, significance was shown in OS when comparing nivolumab with the third-rank avelumab [OS $HR_{indirect}=0.76$; 95% CI (0.60, 0.95); $I^2=0.8\%$], but there was no significant difference between the second-rank agent, atezolizumab, and the third-rank avelumab either in terms of OS, PFS or ORR (Table 4).

In the subgroup NMA among patients with PD-L1 TPS $\geq 1\%$, durvalumab, nivolumab, atezolizumab, and pembrolizumab supposed to be the top-best effective drugs for patients. Durvalumab ranked the best in terms of OS and ORR, with a probability of 35% and 55%, respectively (Figure 4C,S5). Nivolumab was the best among all treatments with a probability of 47% in PFS (Figure 4D). Both of durvalumab and nivolumab were significantly superior to atezolizumab in ORR [ORR $RR_{indirect}=2.52$; 95% CI (1.16, 5.47); ORR $RR_{indirect}=1.73$; 95% CI (1.16, 2.58); $I^2=15\%$], but the superiority of durvalumab or nivolumab to pembrolizumab was insignificant either in terms of OS, PFS or ORR (Table 4). Of note, there was no significant difference between durvalumab and nivolumab either in terms of OS, PFS or ORR.

Atezolizumab ranked third in terms of OS in the population with PD-L1 TPS $\geq 1\%$, and pembrolizumab took third place in terms of ORR (Figure 4C,S5). Because of the lacking data of atezolizumab, pembrolizumab also appeared to be the third-best effective agent with a probability of 51% in terms of PFS temporarily. However, other than the results in terms of ORR, which showed significant inferiority in efficacy for atezolizumab to pembrolizumab [ORR $RR_{indirect}=0.58$; 95% CI (0.36, 0.94); $I^2=15\%$], there was no significant difference between atezolizumab and pembrolizumab on their efficacy (Table 4). All of the heterogeneity between studies in the above NMAs in this setting was measured to be low or medium in terms of the I-square test.

Drug safety

First-line settings

Safety profiles were evaluated in the populations consisting of patients who had received more than one dose of treatment in each study. In the first-line settings, PD-1/L1 inhibitors, either used as monotherapy or combined therapy, showed greater toxicity than chemotherapy alone, as indicated in the pooled RR with SAEs [SAE $RR_{pooled}=1.23$; 95% CI (1.15, 1.31); $I^2=48\%$] as well as respiratory and thoracic disorders [respiratory and thoracic disorders $RR_{pooled}=1.65$; 95% CI (1.41, 1.93); $I^2=51\%$] (Figure S6A,B).

According to the NMAs, pembrolizumab combined

chemotherapy was the best choice among all PD-1/L1 inhibitor therapies for the reduction of both incidences of SAEs and respiratory and thoracic disorders among the top three regimens (pembrolizumab combined with chemotherapy, atezolizumab combined with chemotherapy, and pembrolizumab monotherapy) in terms of efficacy in the first-line settings (Figure 5A,B). Its superiority to atezolizumab combined therapy was both significant in terms of reducing the incidence of SAEs and respiratory and thoracic disorders [SAE $RR_{indirect}=0.78$; 95% CI (0.64, 0.94); $I^2=14\%$; respiratory or thoracic disorders; $RR_{indirect}=0.56$; 95% CI (0.36, 0.89); $I^2=7\%$]. Safety comparisons between pembrolizumab combined therapy and its monotherapy were also shown to be of significance in terms of respiratory and thoracic disorders [respiratory or thoracic disorders; $RR_{indirect}=0.47$; 95% CI (0.31, 0.72); $I^2=7\%$], but results were insignificant in terms of SAEs [SAE $RR_{indirect}=0.91$; 95% CI (0.76, 1.09); $I^2=14\%$] (Table 3). Besides, pembrolizumab monotherapy tended to be safer than atezolizumab combined therapy in terms of SAEs, but atezolizumab showed greater benefits for patients in abating incidences of respiratory and thoracic disorders, however, with no significance both (Figure 5A,B; Table 3). All of the heterogeneity between studies in the above pair-wise analyses and NMAs was measured to be low or medium in terms of the I-square test.

Second- or further-line settings

As indicated in pooled RRs, PD-1/L1 inhibitors were found to be prone to increase the incidence of SAEs compared to chemotherapy [SAE $RR_{pooled}=1.06$; 95% CI (0.99, 1.15); $I^2=8\%$] (Figure S6C), which was similar to the incidence of respiratory and thoracic disorders [respiratory and thoracic disorders $RR_{pooled}=1.48$; 95% CI (1.24, 1.76); $I^2=37\%$] (Figure S6D). Sensitivity analyses were conducted based on the above analyses. By excluding POPLAR, a study with a relatively smaller sample size than OAK, the extent of hazards that patients would suffer from SAEs slightly increased. Besides, patients were much more likely to develop respiratory and thoracic disorders after using PD-1/L1 inhibitors than chemotherapy after omitting CheckMate078, which had included a relatively young patient population.

According to the NMAs, durvalumab was the most toxic agent for patients no matter in terms of SAEs or respiratory and thoracic disorders among the top regimens (durvalumab, nivolumab, atezolizumab, and pembrolizumab) in terms of efficacy in the second- or further-line settings. In contrast, nivolumab ranked as the safest inhibitor in reducing

Table 4 Results of indirect comparisons in the second- or further-line settings

Regimens	OS: HR (95% CI)		PFS: HR (95% CI)		ORR: RR (95% CI)		SAE: RR (95% CI)	Respiratory/thoracic disorders: RR (95% CI)
	ITT population	Subgroups (TPS)	ITT population	Subgroups (TPS)	ITT population	ITT population		
Durvalumab vs. Nivolumab	-	≥1%: 1.00 (0.64, 1.56)	-	≥1%: 1.03 (0.66, 1.61)	1.45 (0.66, 3.20)	1.41 (0.81, 2.45)	5.65 (1.30, 24.60)*	
Durvalumab vs. Atezolizumab	-	≥1%: 0.97 (0.60, 1.57)	-	-	2.52 (1.16, 5.47)*	1.50 (0.88, 2.56)	3.23 (0.72, 14.52)	
Durvalumab vs. Pembrolizumab	-	≥1%: 0.95 (0.62, 1.45)	-	≥1%: 0.86 (0.58, 1.28)	1.47 (0.35, 3.37)	1.41 (0.81, 2.44)	4.48 (1.00, 20.13)	
Durvalumab vs. Avelumab	-	≥1%: 0.69 (0.44, 1.09)	-	≥1%: 0.71 (0.46, 1.10)	1.75 (0.76, 4.06)	1.38 (0.79, 2.42)	4.06 (0.89, 18.50)	
Nivolumab vs. Atezolizumab	0.87 (0.72, 1.06)	≥1%: 0.98 (0.69, 1.37)	0.84 (0.71, 0.99)*	-	1.73 (1.16, 2.58)*	1.07 (0.89, 1.28)	0.57 (0.40, 0.81)*	
Nivolumab vs. Pembrolizumab	-	≥1%: 0.95 (1.73, 1.45)	-	≥1%: 0.84 (0.64, 1.09)	1.01 (0.61, 1.67)	1.00 (0.80, 2.44)	0.79 (0.56, 1.12)	
Nivolumab vs. Avelumab	0.76 (0.60, 0.95)*	≥1%: 0.70 (0.52, 0.93)*	0.79 (0.61, 1.03)	≥1%: 0.69 (0.49, 0.95)*	1.21 (0.72, 2.01)	0.98 (0.77, 1.25)	0.72 (0.48, 1.08)	
Atezolizumab vs. Pembrolizumab	-	≥1%: 0.97 (0.72, 1.32)	-	-	0.58 (0.36, 0.94)*	0.94 (0.80, 1.10)	1.39 (0.87, 2.20)	
Atezolizumab vs. Avelumab	0.87 (0.70, 1.07)	≥1%: 0.71 (0.51, 1.00)	0.94 (0.73, 1.22)	-	0.70 (0.43, 1.13)	0.92 (0.76, 1.11)	1.25 (0.75, 2.09)	
Pembrolizumab vs. Avelumab	-	≥1%: 0.73 (0.57, 0.95)*	-	≥1%: 0.82 (0.63, 1.07)	1.19 (0.67, 2.12)	0.98 (0.78, 1.24)	0.90 (0.54, 1.51)	

* indicates a statistical significance in each indirect comparison. ITT population, intention-to-treat population; TPS, tumor proportion score; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; SAEs, severe adverse events; HR, hazard ratio; RR, relative risk.

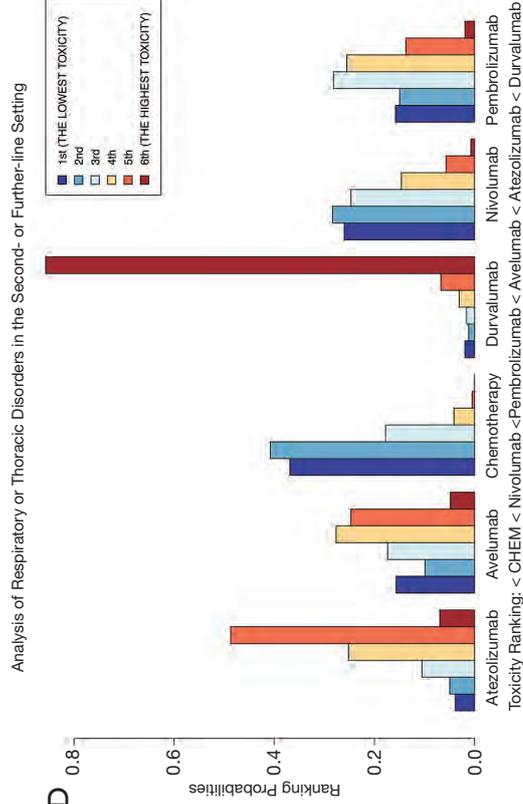
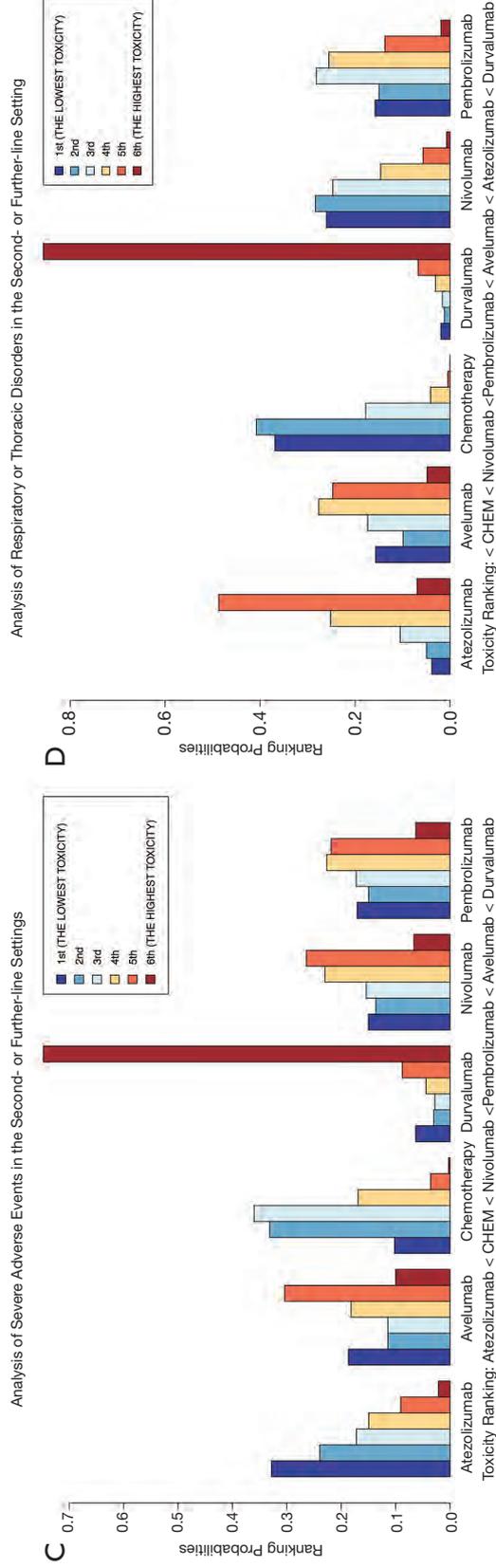
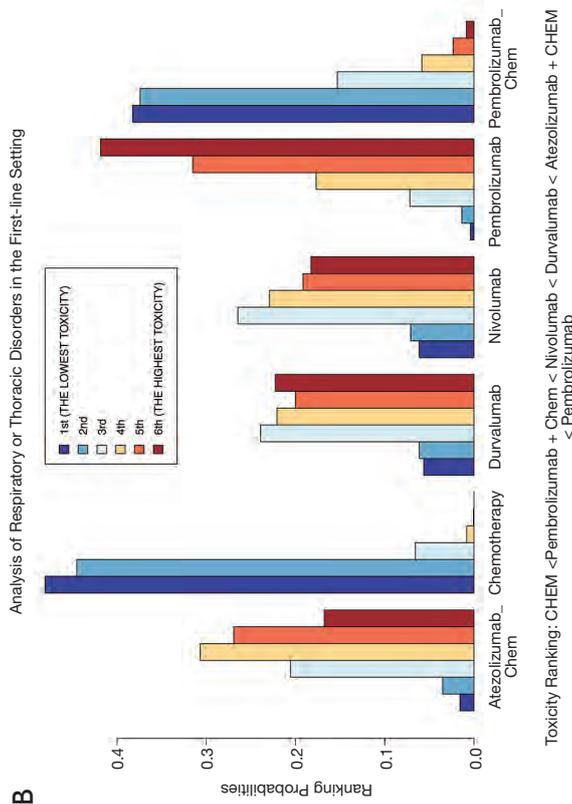
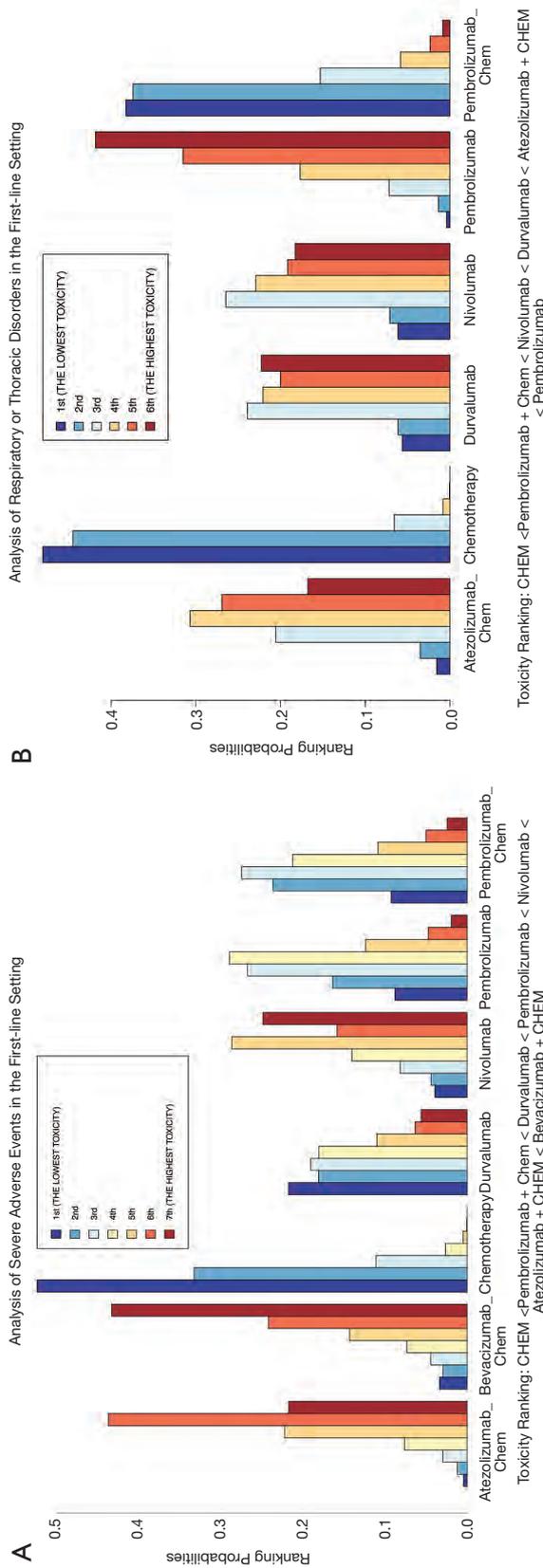


Figure 5 Rankograms of safety analyses with PD-1/L1 inhibitors. (A) Incidence of severe adverse events (SAEs) in the first-line settings; (B) incidence of respiratory and thoracic disorders in the first-line settings; (C) incidence of SAEs in the second- or further-line settings; (D) incidence of respiratory and thoracic disorders in the second- or further-line settings.

the incidence of respiratory and thoracic disorders, and atezolizumab seemed to be the safest agent in terms of SAEs (*Figure 5C,D*). Safety comparisons between nivolumab and atezolizumab were shown to be significant in terms of respiratory and thoracic disorders [respiratory or thoracic disorders; $RR_{\text{indirect}}=0.57$; 95% CI (0.40, 0.81); $I^2=15\%$], but results were insignificant in terms of SAEs (*Table 4*). Besides, atezolizumab tended to be safer than pembrolizumab in terms of SAEs, but pembrolizumab showed greater benefits for patients in abating incidences of respiratory and thoracic disorders, however, with no significance in both of these results (*Figure 5C,D; Table 4*). All of the heterogeneity between studies in the above NMAs was measured to be low in terms of the I-square test.

Discussion

Immunotherapy represents a novel approach in management for patients with NSCLC, in which several ICIs are currently being investigated (45). One of the most studied immune checkpoints is PD-1 together with its ligand PD-L1. PD-1 is transcriptionally induced on activated T cells, and PD-L1 expression is found in multiple tumors including 20–65% of NSCLC (46). To date, three common ICIs, including nivolumab, pembrolizumab, and atezolizumab, have been approved for treatments for lung cancer (36,47,48), while durvalumab and avelumab are still in their clinical development stages. The approvals were based on the improvement in OS and better safety profiles comparing anti-PD-1/L1 agents to other regimens such as chemotherapy, which was reported in RCTs. However, there scarcely exists head-to-head trial evidence or an authoritative guideline for clinicians to determine an optimal agent for diverse patients with NSCLC. Given this condition, NMA could be used to compare these agents by combining direct comparisons with indirect ones using results from the RCTs in a network simultaneously (49,50).

According to results from efficacy NMA and indirect comparisons in the first-line settings, pembrolizumab combined therapy seemed to be the best option in terms of efficacy for advanced NSCLC ITT patients and those with PD-L1 TPS $\geq 1\%$. Pembrolizumab was the optimal choice for those patients whose tumors harbor PD-L1 TPS $\geq 50\%$. Safety NMAs in this setting showed decreasing risks of SAEs for pembrolizumab combined therapy as well as its monotherapy compared to their counterparts. Combining principal outcomes of efficacy and safety, including OS and PFS as well as the incidence of SAEs,

we concluded that the addition of pembrolizumab to chemotherapy was an appropriate choice for patients with positive tumor expressions of PD-L1 (TPS $\geq 1\%$). Patients with high expressions of PD-L1 (TPS $\geq 50\%$) could adopt pembrolizumab alone for better outcomes in clinical practice. In order to compare the advantages and disadvantages of each regimens more comprehensively, efficacy-and-safety-inclusive advantages of each regimen from our analyses were presented with stacked bar charts, in which averages of the first- and second-best ranking probabilities in terms of efficacy (OS and PFS) and safety (SAEs) were accumulated together (*Figures 6A,B,S7*).

Given results from NMAs in the second- or further-line settings, nivolumab and durvalumab became the most two preferred inhibitors in terms of drug efficacy for advanced NSCLC patients, regardless of the PD-L1 status of their tumors. Atezolizumab and pembrolizumab were alternative options because the results of indirect comparisons between nivolumab and them each were not all significant. Considering drug safety profiles, atezolizumab was the most tolerable inhibitor for advanced NSCLC patients in terms of SAEs, whereas nivolumab was the safest agent in terms of respiratory and thoracic disorders, and also it was the second-safest drug in terms of SAEs. Pembrolizumab was less safe than nivolumab either in terms of SAEs or respiratory and thoracic disorders, but it could bring less incidence of respiratory and thoracic disorders than atezolizumab to advanced NSCLC patients. In contrast, durvalumab was surprisingly the most toxic anti-PD-1/L1 drug in terms of SAEs as well as respiratory and thoracic disorders. Combining principal outcomes of efficacy and safety, including OS and PFS or ORR as well as the incidence of SAEs, nivolumab was the most appropriate PD-1/L1 inhibitor for patients who had failed in previous chemotherapies, regardless of the expression of PD-L1 of their tumors. Durvalumab could also be recommended for these patients only if they had relatively good performances. Atezolizumab was an alternative for patients with a generally poor clinical condition without severe pulmonary symptoms. Stacked bar charts incorporating accumulated averages of the first- and second-best ranking probabilities in terms of efficacy (OS and PFS or ORR) and safety (SAEs) are displayed to present the comprehensive advantages of each regimen in these settings (*Figure 6C,D*).

Our NMA is not the first such analysis, but we included avelumab and durvalumab for the first time, and we also incorporated the latest updated data of all included studies. To the best of our knowledge, our study is the

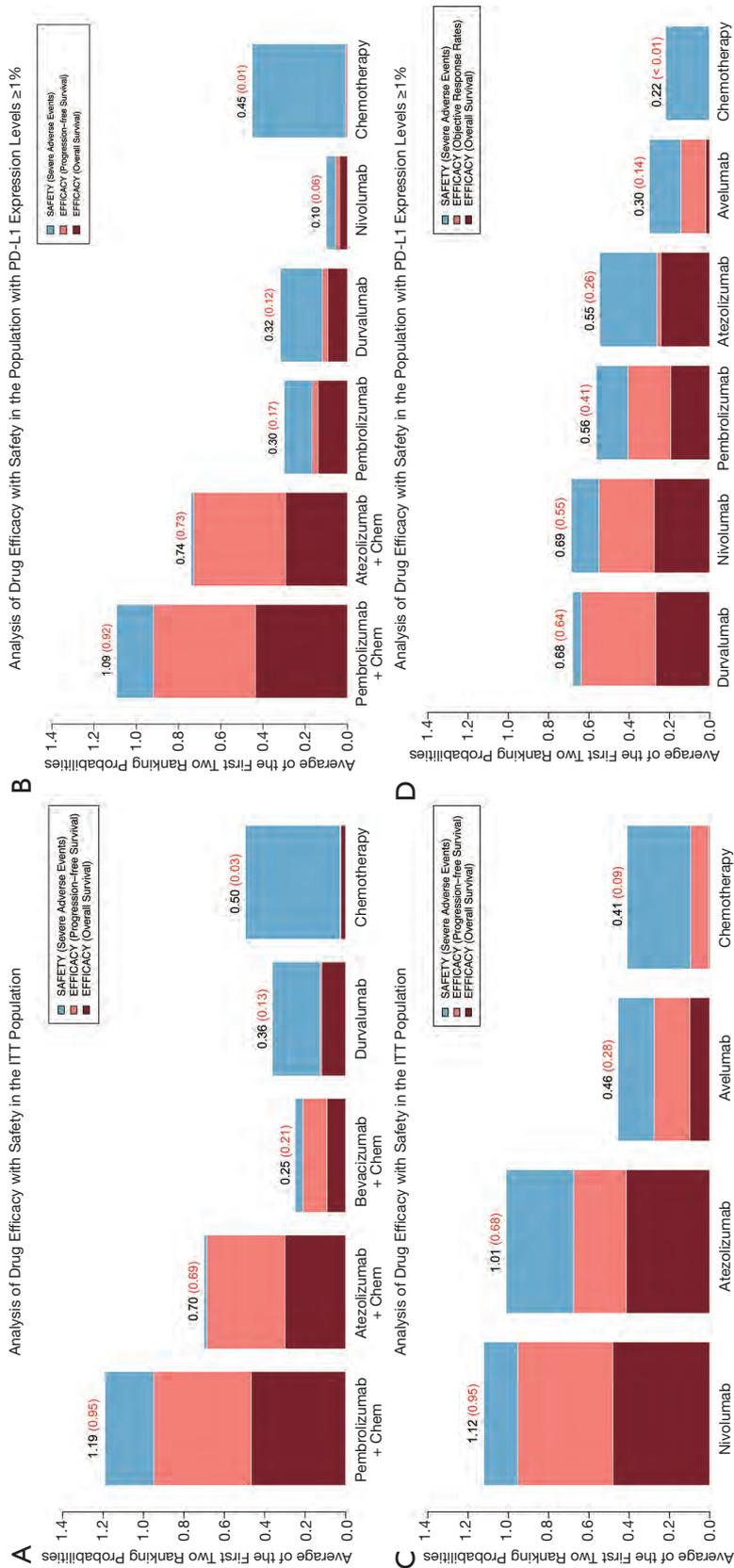


Figure 6 Stacked bar charts of the average of first two leading ranking probabilities with PD-1/L1 inhibitors. (A) Accumulated probabilities in terms of overall survival (OS), progression-free survival (PFS), and the incidence of severe adverse events (SAEs) in the ITT patient population in the first-line settings; (B) accumulated probabilities in terms of OS, PFS, and the incidence of SAEs in the patient population with tumor proportion score (TPS) of PD-L1 ≥ 1% in the first-line settings; (C) accumulated probabilities in terms of OS, PFS, and the incidence of SAEs in the ITT patient population in the second- or further-line settings; (D) accumulated probabilities in terms of OS, objective response rates (ORRs), and the incidence of SAEs in the patient population with TPS of PD-L1 ≥ 1% in the second- or further-line settings.

most comprehensive analysis involving all treating lines confined with chemotherapeutic drugs and PD-1/L1 inhibitors. Despite these strengths, there have been several controversies. Three studies associated with NMA had been conducted to figure out the best PD-1/L1 inhibitor for advanced NSCLC patients in the first-line settings (51-53). Our results were generally consistent with the previous studies, which had all indicated the combination of pembrolizumab to be better than other combined therapies or chemotherapies for patients with relatively high expression of PD-L1. However, atezolizumab and chemotherapy had also been reported to be appropriate for this subset of patients in one of these studies (52). Controversy might have resulted from the insufficient data of atezolizumab in our study, which was partly due to the exclusion of study Impower132, whose results had only been reported at a conference, with interim outcomes. In this case, we further analyzed the efficacy results of atezolizumab combined therapy in our study with the studies Impower 130 and 131. We found that although the front-ranking probabilities of atezolizumab combined therapy were relatively high in patients with positive PD-L1 expression (TPS $\geq 1\%$), it was still significantly less beneficial for patients than pembrolizumab combined therapy according to the results from indirect comparisons. Safety analyses reported that this combined regimen seemed to be significantly less safe than pembrolizumab combined therapy. We, therefore, believe that the combination of atezolizumab and chemotherapy is indeed inferior to the pembrolizumab combined therapy when considering efficacy and safety together, but the results still need validations by RCTs in the future. Besides, five studies had been performed to compare PD-1/L1 inhibitors in the subsequent settings (54-58). Drug efficacy was the primary outcomes reported at the end of these studies while only a few studies focused on drug safety. Nivolumab was recommended consistently by almost all of these five studies, four of which also suggested pembrolizumab with no significant difference reported between these two regimens (54-56,58). The comparison on drug safety between these two drugs had only been analyzed by one study, which had reported that pembrolizumab had a higher incidence of adverse effects than nivolumab, which was consistent with our results (54). Atezolizumab had been recommended by the authors in three of these previous studies (55-57), which was also consistent with our study.

There were still some limitations in our study. First, there have been two existing parameters for the testing

of PD-L1 expression cut-offs, tumor cell and tumor-infiltrating immune cell staining, and the cut-offs also varied in different studies. In our study, the included trials were shown to use one or both of these two methods, whereas in several trials, researchers had not completely clarified the parameters that had been measured. Thus, caution must be used when interpreting subgroup results. Second, nine included studies only reported interim results in OS. Because immunotherapy requires a longer follow-up to manifest its benefits on patient survival, this limitation might lead to effects on the final pooled and indirect results. Hence, it is a necessity to perform further analyses in the future. Third, two dosages of drugs had been evaluated in the included study Keynote 010, involving 2 and 10 mg/kg, which could lead to a relative overestimation of the drug-related toxicity as well as efficacy in the second- or further-line settings, because the dosage of 2 mg/kg is currently approved for clinical use. Thus, the efficacy and safety profiles of pembrolizumab compared to other inhibitors need to be validated by further research. Fourth, subgroup analyses related to the histological types of NSCLC on the regimens were not carried out in this work, because outcomes of patients with different histological types were hardly reported in the included studies according to reported details of each included study. Moreover, the pooled and indirect results associated with atezolizumab combined therapy in the first-line settings among patients with PD-L1 TPS $\geq 1\%$ only involved those with squamous histology, leading to the only potential heterogeneity and non-transitive result in our study. Thus, it might be an interesting issue for researchers to analyze that whether the survival of NSCLC patients with various histological types differs after treated with PD-1/L1 inhibitors. Fifth, SAEs which were defined as interferes with normal life functions or events requiring extending inpatient hospitalization were subjective and might have contributed to the observer bias because the trials were all open-label. In addition, the degree of classifications in respiratory and thoracic disorders varied between studies; for example, categories of disorders in larger clinical studies with more patients involved appeared to be more detailed. Our results were therefore suggestive but not conclusive, and caution is recommended in the interpreting. Head-to-head clinical trials comparing these emerging PD-1/L1 inhibitors are still a necessity to reduce the limitations from indirect comparisons, to identify the optimal treatments for advanced NSCLC. Last but not least, we did not include any anti-CTLA-4 drugs in our analyses. Since CTLA-4 is another pivotal

checkpoint which is practical for anticancer therapies, and the combination of CTLA-4 and PD-1 inhibitors has been suggested to have synergistic effect on the activation of anti-tumor immune response and to increase the response rates in patients, multiple studies have investigated the efficacy of anti-PD-1/L1 combined with anti-CTLA-4 antibodies in lung cancer (59-62). Thus, the differences in efficacy and safety between this combined therapy and that analyzed by us should also be assessed by further studies. Besides, other combination therapies that contain more than one checkpoint inhibitors are also worthy of assessment in the field of managements for advanced NSCLC patients.

Conclusions

The drug efficacy of regimens including PD-1/L1 inhibitors is superior to chemotherapy for NSCLC, regardless of the therapeutic line used. The monotherapy of these inhibitors seemed to be inferior to that of the combination therapy. When using PD-1/L1 inhibitors in the clinical practice, PD-L1 expression status, physical conditions, and whether they have received systemic therapy should all be considered for patients. Pembrolizumab in combination with chemotherapeutic drugs is appropriate for patients with a low expression of PD-L1, while patients with a high expression of PD-L1 can also choose pembrolizumab alone for better clinical outcomes. In the second- or further-line settings, nivolumab is an optimal choice for patients with advanced NSCLC. The novel inhibitor, durvalumab, can only be tried by patients with relatively good physical performances for better clinical outcomes. Atezolizumab would be an alternative for patients with poor general conditions, but it should not be suggested when thoracic disorders have already occurred in them. However, our results need to be further validated in future clinical trials.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approval was exempted by the Institutional Review Committee of Zhongshan Hospital, Fudan University, Shanghai, China (approval number: B2019-232R).

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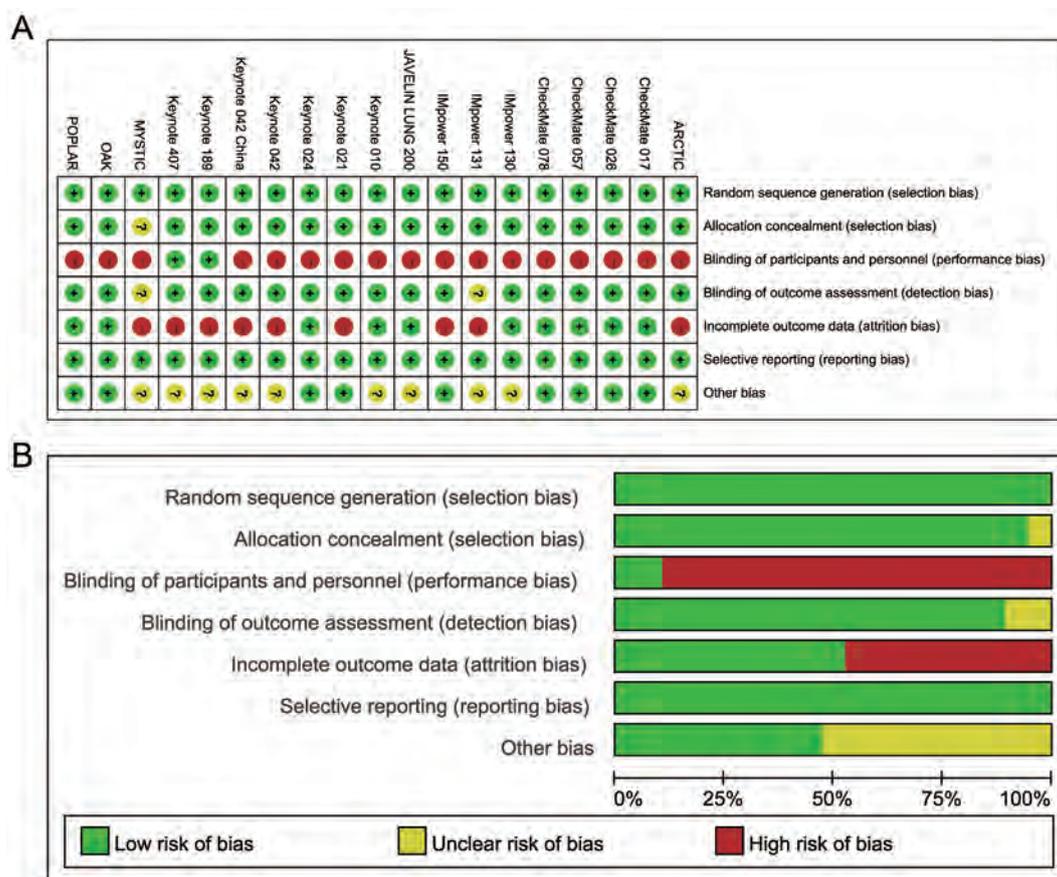


Figure S1 Risk of bias assessment. (A) Risk of bias in individual studies; (B) risk of bias across included studies.

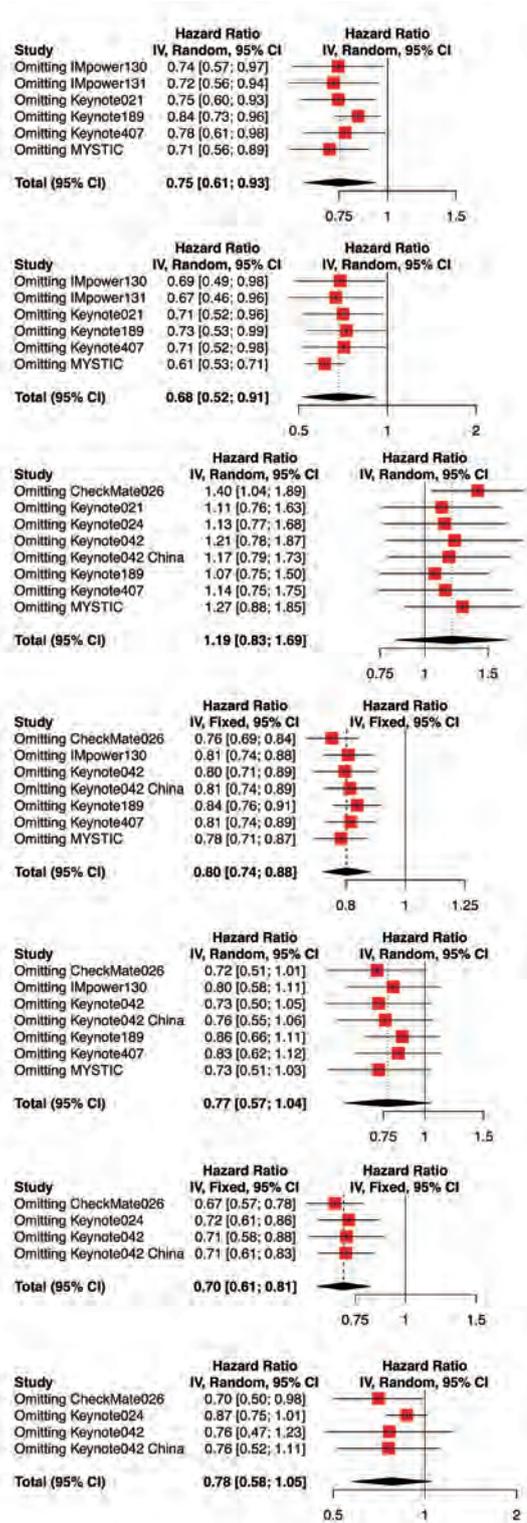
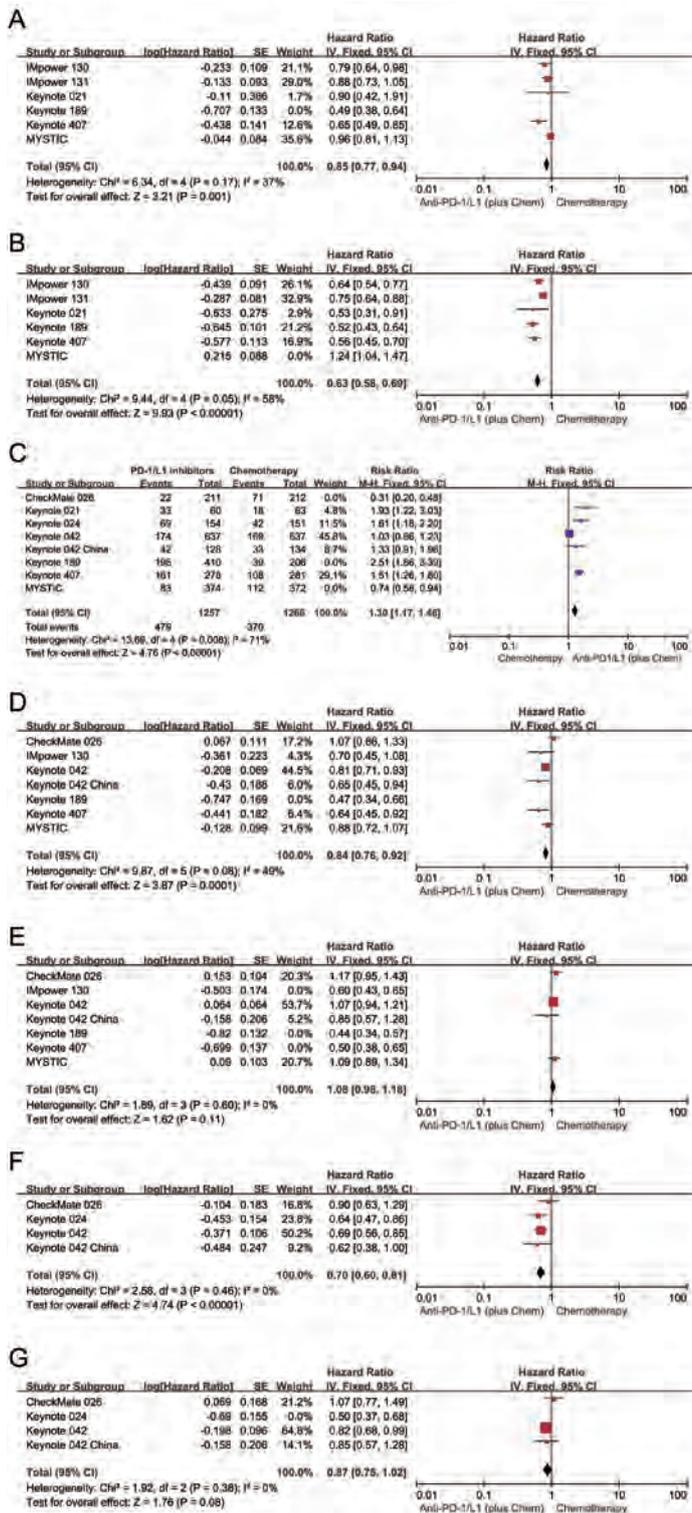


Figure S2 Forest plots and sensitivity analyses of efficacy analyses with PD-1/L1 inhibitors in the first-line settings. (A) Overall survival (OS) in the intention-to-treat (ITT) patient population; (B) progression-free survival (PFS) in the ITT patient population; (C) objective response rate (ORR) in the patient population who had received more than one dose of treatment; (D) OS in the patient population with tumor proportion score (TPS) of PD-L1 $\geq 1\%$; (E) PFS in the patient population with PD-L1 TPS $\geq 1\%$; (F) OS in the patient population with PD-L1 TPS $\geq 50\%$; (G) PFS in the patient population with PD-L1 TPS $\geq 50\%$.

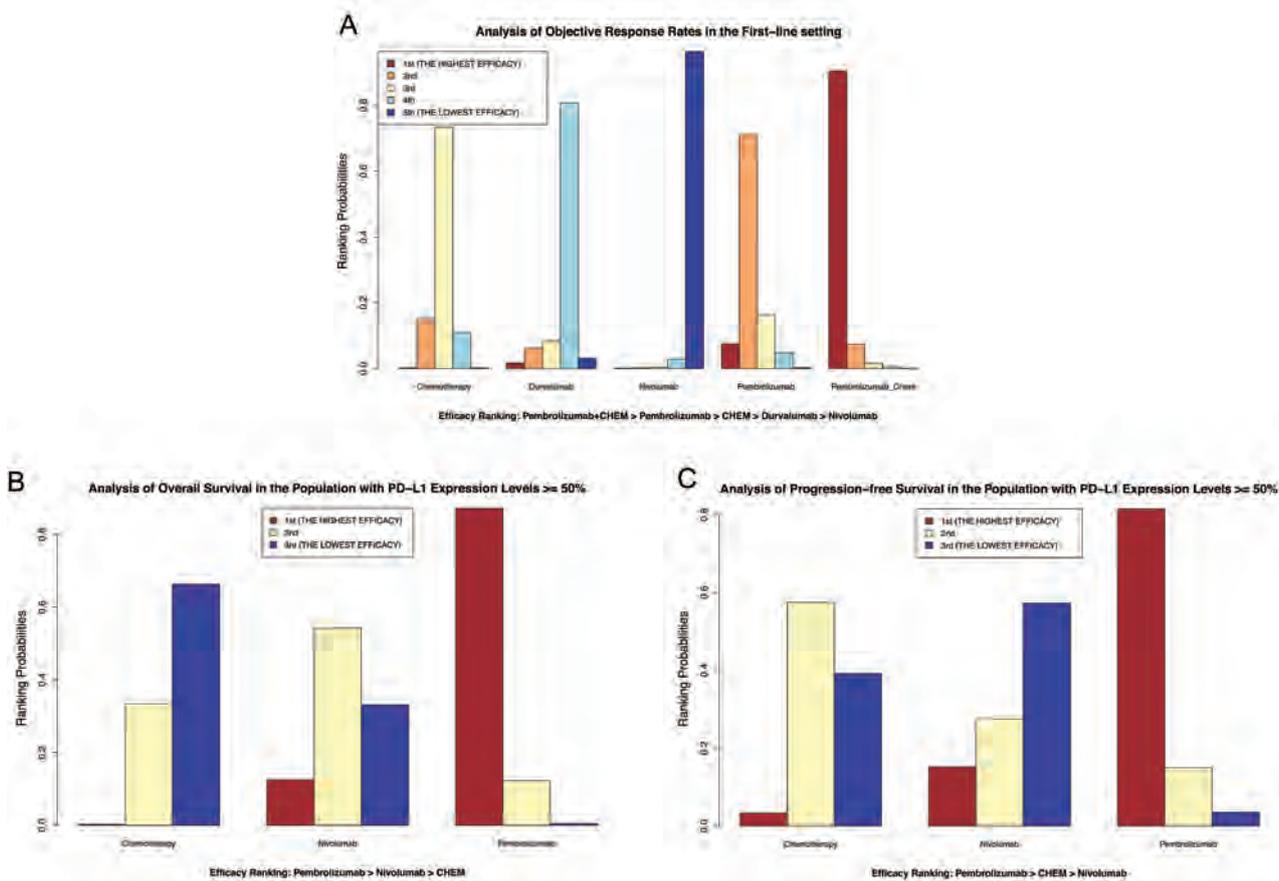


Figure S3 Rankograms of efficacy analyses with PD-1/L1 inhibitors. (A) Objective response rate (ORR) in the patient population who had received more than one dose of treatment in the first-line settings; (B) overall survival (OS) in the patient population with PD-L1 TPS \geq 50% in the first-line settings; (C) progression-free survival (PFS) in the patient population with PD-L1 TPS \geq 50% in the first-line settings.

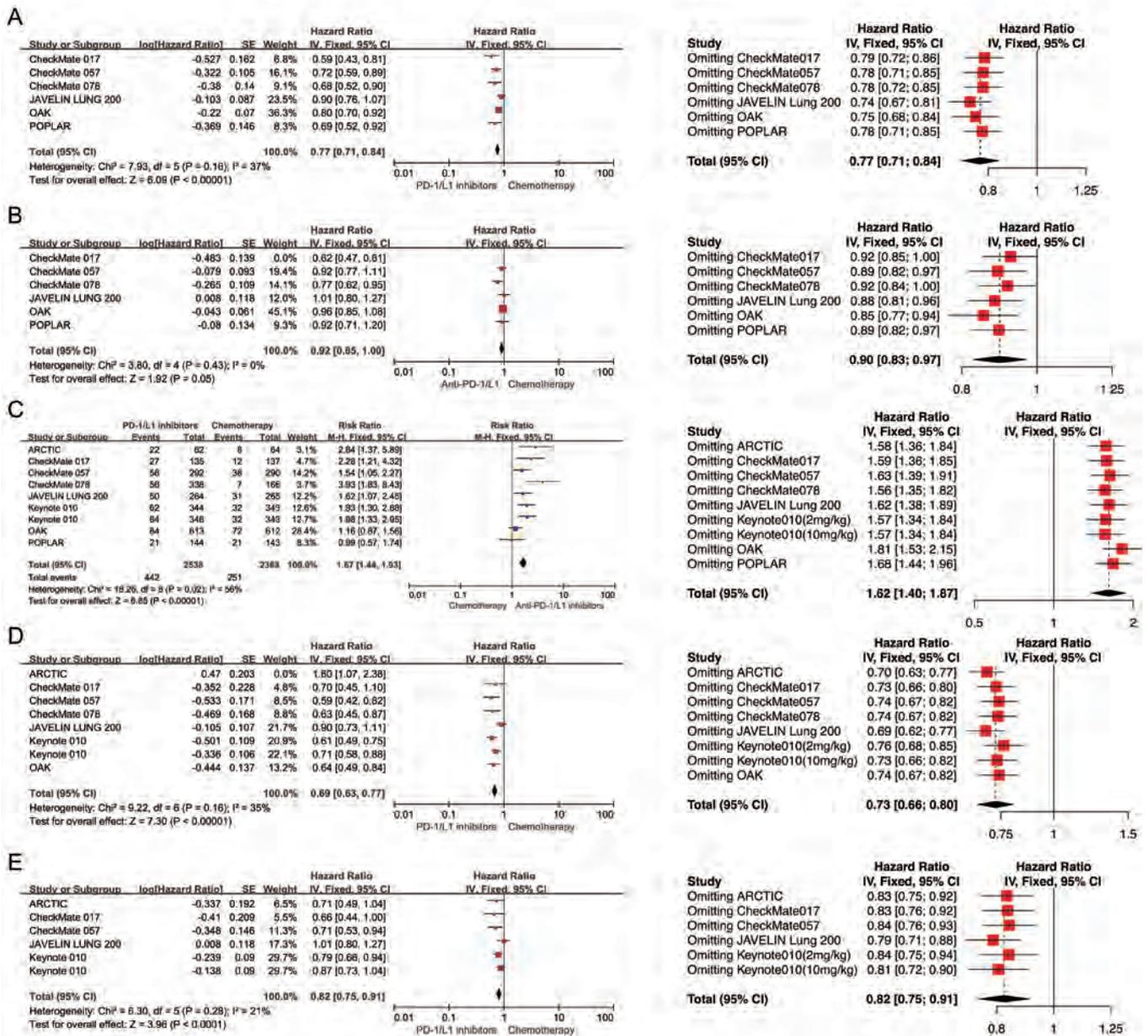


Figure S4 Forest plots and sensitivity analyses on efficacy with PD-1/L1 inhibitors in the first-line settings. (A) Overall survival (OS) in the intention-to-treat (ITT) patient population; (B) progression-free survival (PFS) in the ITT patient population; (C) objective response rate (ORR) in the patient population who had received more than one dose of treatment; (D) OS in the patient population with tumor proportion score (TPS) of PD-L1 $\geq 1\%$; (E) PFS in the patient population with PD-L1 TPS $\geq 1\%$.

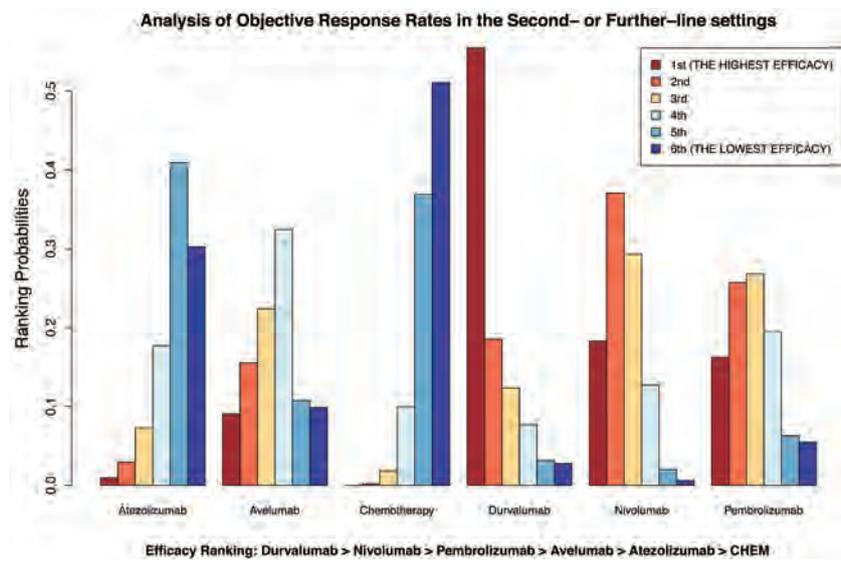


Figure S5 Objective response rate (ORR) in the patient population who had received more than one dose of treatment in the second- or further-line settings.

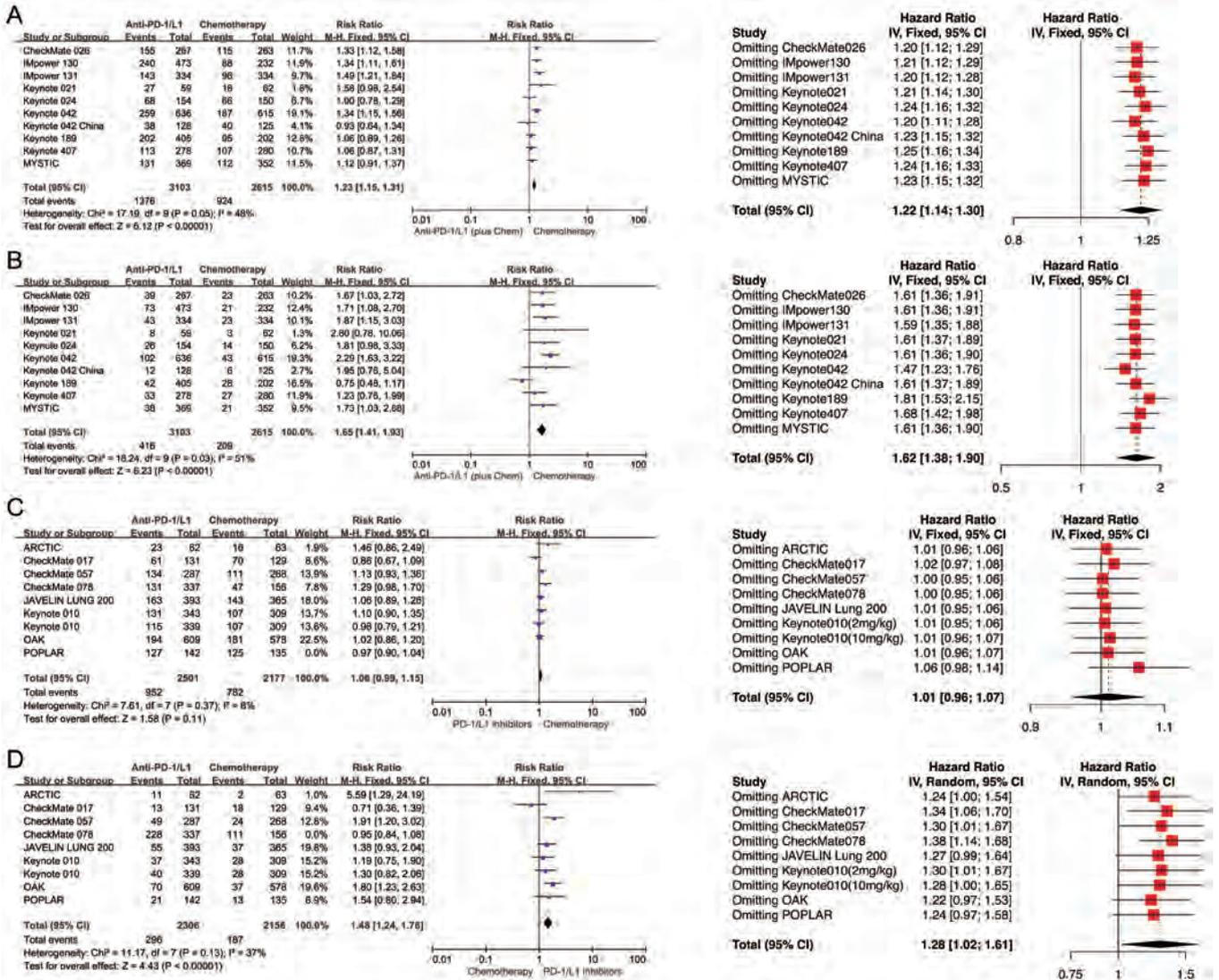


Figure S6 Forest plots and sensitivity analyses on safety with PD-1/L1 inhibitors. (A) Incidence of severe adverse events (SAEs) in the first-line settings; (B) incidence of respiratory and thoracic disorders in the first-line settings; (C) incidence of SAEs in the second- or further-line settings; (D) incidence of respiratory and thoracic disorders in the second- or further-line settings.

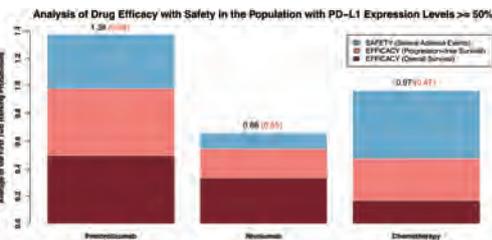


Figure S7 The stacked bar chart of the average of first two leading ranking probabilities with PD-1/L1 inhibitors. Accumulated probabilities in terms of overall survival (OS), progression-free survival (PFS), and the incidence of severe adverse events (SAEs) in the patient population with tumor proportion score (TPS) of PD-L1 $\geq 50\%$ in the first-line settings.