

Feasibility and safety of PD-1/L1 inhibitors for non-small cell lung cancer in front-line treatment: a Bayesian network meta-analysis

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Background: This Bayesian network meta-analysis (NMA) was conducted to compare efficacy and safety of programmed death 1/ligand 1 (PD-1/L1) inhibitors in previous untreated advanced non-small cell lung cancer (NSCLC) patients.

Methods: Eligible studies evaluating first-line anti-PD-1/L1 based regimens in advanced NSCLC patients were included. Overall survival (OS), progression free survival (PFS), objective response rate (ORR), as well as treatment-related severe adverse events (tr-SAE) were synthesized within the Bayesian framework. Subgroup analysis was conducted according to PD-L1 expression.

Results: Twelve studies including 7,490 patients and 9 treatment strategies were enrolled in this study. For the PD-L1 expression non-selective patients, all chemo-immunotherapies were significantly better than chemotherapy for prolonging OS and PFS, except for cemiplizumab plus chemotherapy (HR =0.72) failed to show advantages for OS. In addition, pembrolizumab plus chemotherapy showed better PFS than nivolumab plus ipilimumab (HR =0.66). In PD-L1 $\geq 50\%$ patients, all immunotherapy was better than chemotherapy for OS, except for nivolumab (HR =0.83) and nivolumab plus ipilimumab (HR =0.70). For PFS, pembrolizumab plus chemotherapy (HR =0.39), atezolizumab plus chemotherapy (HR =0.47) and pembrolizumab (HR =0.67) were significantly better than chemotherapy. In PD-L1 1–49% patients, pembrolizumab plus chemotherapy (HR =0.52) and atezolizumab plus chemotherapy (HR =0.70) were better than chemotherapy for PFS. In the PD-L1 positive or negative group, all included corresponding regimens were equivalence according to OS and PFS.

Conclusions: We conducted a systematic comparison of first line immunotherapy for advanced NSCLC. Chemo-immunotherapies were better than chemotherapy and mono-immunotherapies in most patients. Pembrolizumab might have better efficacy than other PD-1/L1 inhibitors.

Keywords: PD-1/L1 inhibitors; non-small cell lung cancer (NSCLC); front-line; network meta-analysis (NMA)

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Introduction

Non-small cell lung cancer (NSCLC) occupies 85% of all lung cancer cases (1). The majority of NSCLC patients are diagnosed at advanced stage and the prognosis for these patients is poor, therefore systematic therapy is the primary choice. Nearly 30–40% NSCLC patients owned sensitive mutations, that may suitable for corresponding tyrosine kinase inhibitors. However, effective treatments for other patients without mutations are rather limited. The response rate of traditional chemotherapy is only 15–30% (2).

Programmed death 1/anti-programmed death ligand 1 (PD-1/L1) as an inhibitory pathway detected in various malignant tumors that regulates the function of autoimmunity to against tumors, therefore the inhibitors of PD-1/L1 pathway started a new era of cancer treatment (3,4). Except for FDA approved PD-1/L1 inhibitors in NSCLC (nivolumab, pembrolizumab, atezolizumab and durvalumab), many other agents with ongoing clinical trials also demonstrated satisfactory efficacy and safety for advanced NSCLC.

Recently, a series of randomized controlled trials (RCTs) demonstrated significant clinical benefits in front line treatment for NSCLC using PD-1/L1 inhibitors, including longer time-to-event outcomes and less side effects (5-7). However, no head-to-head clinical trial has ever compared which PD-1/L1 agent or strategy is the optimal choice. In addition, there is no study comparing the efficacy of PD-1/L1 inhibitors according to PD-L1 expression.

To address this gap, we performed a Bayesian network meta-analysis (NMA) of RCTs to compare these strategies for untreated advanced NSCLC, attempting to identify the optimal treatment.

Methods

Search strategy

Systematic search was conducted through PubMed and Web of Science to select RCTs before 1 January 2020. Keywords: NSCLC, first-line, front-line, PD-1, PD-L1, atezolizumab, cemrlizumab, nivolumab, pembrolizumab and the name of other PD-1/L1 inhibitors. We also screened EMSO, ASCO, and WCLC of recent years to avoid missing updated data. This NMA was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA extension statement for NMAs.

Selection criteria

The inclusion criteria of this NMA were as follow: (I) RCTs; (II) PD-1/L1 inhibitors as first-line therapy; (III) comparison between chemotherapy and immunotherapy or their combinations; (IV) completed outcomes. Exclusion criteria: (I) studies included patients that received other therapies in front-line other than chemotherapy or immunotherapy; (II) studies included patients with EGFR, ALK or other sensitive mutations; (III) systematic reviews, meta-analyses, case reports, letters or non-English documents.

Data extraction and quality assessment

Two researchers (Guo Lin and Hengrui Liang) independently conducted the data extraction and the following data were summarized: author, publication year, phase of trials, treatments, number of patients, histology type, gender, age, smoke status, Eastern Cooperative Oncology Group (ECOG) score, objective response rate (ORR), time-to-event outcomes included overall survival (OS) and progression-free survival (PFS), and side effects were more than grade 3 treatment-related severe adverse events (tr-SAE).

The quality assessment was performed using Cochrane risk of bias tools from 7 perspectives: (I) random sequence generation; (II) allocation concealment; (III) blinding of participants and personnel; (IV) blinding of outcome assessment; (V) incomplete outcome data; (VI) selective reporting; (VII) other bias. Disagreements were resolved via discussion among authors.

Statistical analysis

We included all direct and indirect data to compare the efficacies of different therapies. OS and PFS were primary outcomes. ORR and the incidence rate of tr-SAE were secondary outcomes. Hazard ratios (HR) for OS and PFS, odds ratios (OR) for ORR and the incidence rate of tr-SAE were calculated.

Open BUGS (version 3.2.3) software was applied to perform Bayesian network-meta analysis in random-effect model. Based on noninformative uniform and normal prior distributions, we generated 3 chains and used 50,000 iterations with 20,000 burn-ins for each chain (the thinning interval was 10). Moreover, this software can identify the probability of each regimen to be ranked the best,

second best, third best, etc. Based on the surface under the cumulative ranking curves (SUCRA) for aforementioned endpoints, we showed them in ranking plots using Microsoft Excel.

Subgroup analysis was performed according to PD-L1 expression. Network plots were completed based on the connection between eligible trials according to the number of trials and sample size. Traditional pairwise meta-analyses (PWMA) were applied to compare multiple trials and control treatment simultaneously. Heterogeneity was evaluated by chi-square test and I-square test, using random-effect model if p-values <0.05 otherwise fixed-effect model was used. Funnel plots, Begg's and Egger's test were applied for testing publication bias. To ensure the reliability of NMA, sensitive analysis was performed by excluding phase II trials with a small sample size and subgroup analyses also performed in sensitivity analysis. All tests were 2-sided, with an α -level of 0.05.

Results

Study selection and characteristics

We identified 3,781 records from online databases and international conferences. After excluding duplicates and screening for titles/abstracts, 32 studies were reviewed for full-text assessment. Eventually, 12 studies met the selection criteria (Figure 1). All updated data were used in our pooled analysis. The detailed information of study characteristics was summarized in Tables 1-3. Overall, 7,490 patients were enrolled in 9 different treatment strategies (8-19): chemotherapy, pembrolizumab, nivolumab, atezolizumab, pembrolizumab plus chemotherapy, nivolumab plus chemotherapy, atezolizumab plus chemotherapy, carelizumab plus chemotherapy and nivolumab plus ipilimumab.

In total, the networks included 9 treatment strategies for PFS, OS, ORR and tr-SAE. All studies but KEYNOTE-021G (phase II clinical trials) were multi-center phase III clinical trials. All studies were double-arm trials, except for CHECKMATE-227 (four arms): nivolumab, nivolumab plus chemotherapy, nivolumab plus ipilimumab and chemotherapy. See Figure S1 for detailed results of the bias assessment.

NMA in PD-L1 non-selective NSCLC patients

For the PD-L1 expression non-selective population, 5

treatments reported OS (Figure 2A). All combination treatments were significantly better than chemotherapy for prolonging OS, except for carelizumab plus chemotherapy (HR =0.72, 95% CI: 0.49 to 1.04). Among these combination strategies, pembrolizumab plus chemotherapy performed significant better OS than atezolizumab plus chemotherapy (HR =0.75, 95% CI: 0.58 to 0.95) (Figure 2B). Forest plots and contribution plots were presented in Figures S2-S6.

In this subgroup PFS was assessed for 5 treatments (Figure 2A). All combination therapies were significantly better than chemotherapy on PFS, except for nivolumab plus ipilimumab (HR =0.79, 95% CI: 0.61 to 1.02). Additionally, pembrolizumab plus chemotherapy performed notably longer PFS than nivolumab plus ipilimumab (HR =0.66, 95% CI: 0.49 to 0.90) and was equal to atezolizumab plus chemotherapy (HR =0.79, 95% CI: 0.62 to 1.03) and carelizumab plus chemotherapy (HR =0.85, 95% CI: 0.58 to 1.23) (Figure 2B).

Table 4 showed absolute value of pooled ORR of each treatment via single arm meta-analysis. All combination therapy significantly increased the ORR compared with chemotherapy alone except for nivolumab plus ipilimumab (OR =1.29, 95% CI: 0.78 to 2.15). Specially, ORR in pembrolizumab plus chemotherapy was significantly higher than that in atezolizumab plus chemotherapy (OR =1.83, 95% CI: 1.15 to 2.90), nivolumab plus ipilimumab (OR =2.45, 95% CI: 1.33 to 4.54) but similar with carelizumab plus chemotherapy (OR =1.35, 95% CI: 0.69 to 2.63) group (Figure 2B).

Bayesian ranking profiles (Figure 2C) suggested that pembrolizumab plus chemotherapy was most likely to be ranked as first for OS (probability =63%), PFS (probability =74%) and ORR (probability =94%) in PD-L1 expression non-selective NSCLC patients.

Subgroup analysis according to PD-L1 expression

PD-L1 TPS \geq 50%

8 treatments were included in the PD-L1 \geq 50% population (Figure 3). When using mono-immunotherapy, pembrolizumab (HR =0.67, 95% CI: 0.51 to 0.88) and atezolizumab (HR =0.59, 95% CI: 0.36 to 0.95) would significantly prolong OS compared with chemotherapy. Only pembrolizumab had significant benefit compared with chemotherapy according to PFS (HR =0.67, 95% CI: 0.45 to 0.94). No significant survival or response difference

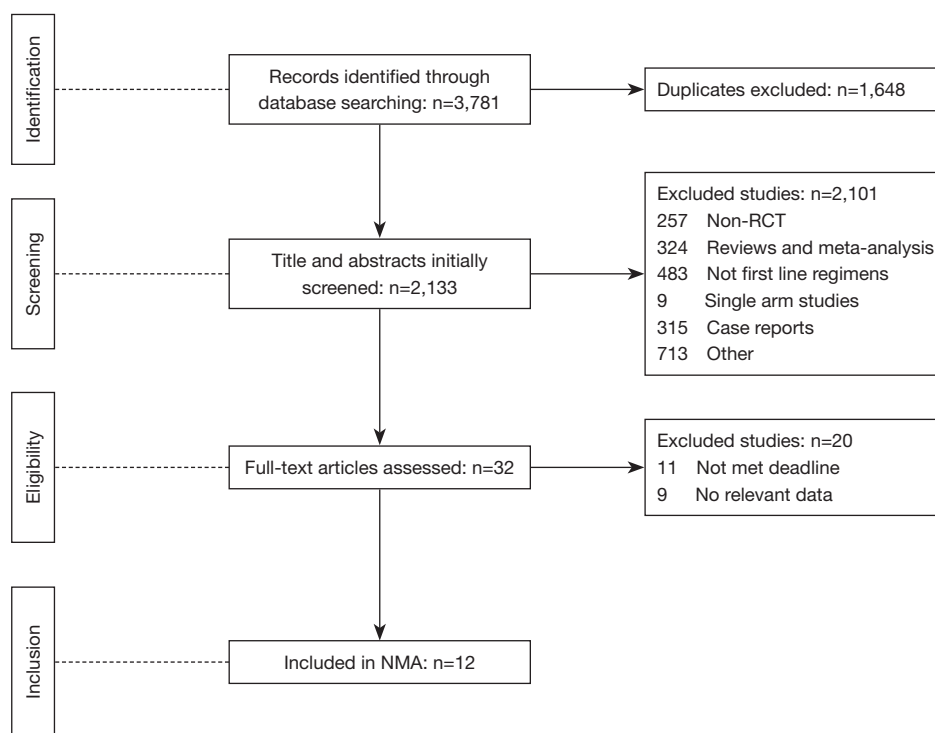


Figure 1 Flowchart of study selection. RCT, randomized controlled trial; NMA, network meta-analysis.

was found among monotherapy of all PD-1/L1 inhibitors (pembrolizumab *vs.* atezolizumab *vs.* nivolumab). As for chemoimmunotherapy, pembrolizumab plus chemotherapy and atezolizumab plus chemotherapy were better than chemotherapy both in OS and PFS. All chemotherapy-based combination strategies performed similar in survival comparison (Figure 4). Table 5 showed absolute value of pooled ORR of each treatment via single arm meta-analysis. As for ORR comparison, Pembrolizumab plus chemotherapy was equal to atezolizumab plus chemotherapy (OR =1.79, 95% CI: 0.68 to 4.74) and superior to any other treatments.

Bayesian ranking profiles (Figure 5) suggested atezolizumab alone was most likely to be ranked as first to offer best OS (probability =41%), caremlizumab plus chemotherapy had the highest possibility to offer best PFS (probability =45%) and pembrolizumab plus chemotherapy was the best possible treatment for ORR (probability =95%).

PD-L1 TPS 1–49%

6 treatments were included for accessing the best strategy in PD-L1 1–49% NSCLC patients (Figure 3B). All included treatments showed similar OS. For PFS, pembrolizumab

plus chemotherapy was similar to atezolizumab plus chemotherapy (HR =0.74, 95% CI: 0.48 to 1.15) and were both better than chemotherapy. Only pembrolizumab plus chemotherapy showed higher ORR than chemotherapy (HR =2.40, 95% CI: 1.04 to 6.15) (Figure 4B).

According to Bayesian ranking profiles (Figure 5), the combination of pembrolizumab and chemotherapy was most likely to be ranked as first to offer best OS (probability =65%), PFS (probability =91%) and ORR (probability =92%).

PD-L1 TPS >1%

For PD-L1 positive expressed advanced NSCLC patients, 8 treatments were included in analysis (Figure 3C). All included regimens showed similar efficacy in this sub-population according to OS and PFS. Pembrolizumab plus chemotherapy significantly increase ORR than nivolumab (HR =4.52, 95% CI: 1.13 to 17.47) and chemotherapy (HR =4.33, 95% CI: 1.38 to 13.25) (Figure 4C).

Bayesian ranking profiles (Figure 5) indicated that the pembrolizumab plus chemotherapy was most likely to be the best regimen for increasing OS (probability =34%), PFS (probability =46%) and ORR (probability =94%).

Table 1 Study and demographical characters of included RCTs

Study name	Publication	Year	Phase	Blind	Stage	Histology	Treatment		Patients (n)	
							Experiment	Control	Experiment	Control
KEYNOTE 021G	AACR	2018	II	Open label	III, IV	Non-squamous	Pembrolizumab + pemetrexed + carboplatin, 4 cycles; followed by pembrolizumab for 24 months + pemetrexed, maintenance therapy	Pemetrexed + carboplatin, 4 cycles; followed by pemetrexed, maintenance therapy	60	63
KEYNOTE 024	WCLC	2019	III	Open label	IV	NSCLC	Pembrolizumab, 35 cycles	Platinum based chemotherapy regimens, 4 to 6 cycles	154	151
KEYNOTE 407	ESMO	2019	III	Double blind	IV	Squamous	Pembrolizumab, 35 cycles; followed by carboplatin + paclitaxel, 4 cycles	Placebo, 35 cycles; followed by carboplatin + paclitaxel, 4 cycles	278	281
KEYNOTE 042	Lan Onco	2019	III	Open label	III, IV	NSCLC	Pembrolizumab, 35 cycles	Platinum based chemotherapy regimens, 4 to 6 cycles; followed by pemetrexed, maintenance therapy	637	637
KEYNOTE 189	ASCO	2019	III	Double blind	IV	Non-squamous	Pembrolizumab, 35 cycles; followed by platinum + pemetrexed, 4 cycles	Placebo, 35 cycles; followed by platinum + pemetrexed, 4 cycles	410	206
CheckMate 026	NEJM	2017	III	Open label	IV, recurrent	NSCLC	Nivolumab, every 2 weeks	Platinum based chemotherapy regimens, 4 cycles; followed by pemetrexed, maintenance therapy	271	270
CheckMate 227	ESMO	2019	III	Open label	IV, recurrent	NSCLC	Nivolumab, every 2 weeks; platinum-based chemotherapy, 4 cycles;	Platinum doublet chemotherapy, 4 cycles	177	186
CAMEL	WCLC	2019	III	Open label	IV	Non-squamous	Caremilizumab + carboplatin + pemetrexed, every 3 weeks	Carboplatin + pemetrexed, 4 to 6 cycles	205	207
IMpower 110	ESMO	2019	III	Open label	IV	NSCLC	Atezolizumab, every 3 weeks	Pemetrexed, best supportive care	277	277
IMpower 130	Lan Onco	2019	III	Open label	IV	Non-squamous	Atezolizumab + carboplatin + nab-paclitaxel, 4 to 6 cycles; followed by atezolizumab, maintenance therapy	Carboplatin + nab-paclitaxel, 4 to 6 cycles; followed by pemetrexed, maintenance therapy or best supportive care	451	228

Table 1 (continued)

Table 1 (continued)

Study name	Publication	Year	Phase	Blind	Stage	Histology	Treatment		Patients (n)	
							Experiment	Control	Experiment	Control
IMpower 131	WCLC	2018	III	Open label	IV	Squamous	Atezolizumab+ carboplatin+ nab-paclitaxel, 4 to 6 cycles; followed by atezolizumab, maintenance therapy	Carboplatin+ nab-paclitaxel, 4 to 6 cycles; followed by best supportive care	343	340
IMpower 132	ESMO & WCLC	2018	III	Open label	IV	Non-squamous	Atezolizumab + platinum + pemetrexed, 4 to 6 cycles; followed by atezolizumab + pemetrexed, maintenance therapy	Platinum + pemetrexed, 4 to 6 cycles; followed by pemetrexed, maintenance therapy	292	286

RCT, randomized controlled trial; TP, cisplatin or carboplatin plus paclitaxel; PC, cisplatin or carboplatin plus pemetrexed; NSCLC, non-small cell lung cancer; NEJM, New England Journal Medicine; ASCO, American Society of Clinical Oncology congress; ESMO, conference of European Society for Medical Oncology congress; WCLC, World conference on lung cancer; Lan Onco, Lancet Oncology; AACR, American Association for Cancer Research.

PD-L1 TPS <1%

6 treatments were included in PD-L1 non-expressed population (Figure 3D). All treatments were equivalence according to OS, PFS and ORR (Figure 4D).

Bayesian ranking profiles (Figure 5) suggested the combination of nivolumab and ipilimumab was the most possible therapy to be ranked as first for OS (probability =45%); pembrolizumab plus chemotherapy had the greatest possibility to favor PFS (probability =25%) and ORR (probability =82%).

Safety analysis

All 12 studies including 9 treatments were involved in tr-SAE NMA (Figure 6A). Table 6 showed the pooled ORR of each treatment via single arm meta-analysis.

All mono-immunotherapy had significant lower tr-SAE than chemotherapy. No significant difference was found among mono-immunotherapies (pembrolizumab vs. atezolizumab vs. nivolumab). All chemotherapy-based regimens had higher tr-SAE than chemotherapy except for pembrolizumab plus chemotherapy (OR =1.17, 95% CI: 0.85 to 1.69). In addition, the tr-SAE of pembrolizumab plus chemotherapy lower than other chemotherapy-based regimens expect for atezolizumab plus chemotherapy (OR =0.67, 95% CI: 0.43 to 1.09) (Figure 6B).

The ranking outcomes (Figure 6C) suggested that atezolizumab monotherapy had the lowest opportunity (probability =2.2%) to confront tr-SAE among all mono-immunotherapies. Pembrolizumab plus chemotherapy had the lowest possibility (probability =59%) among chemotherapy-based combination therapies.

Sensitivity analysis and publication bias

We performed sensitivity analysis after excluding KEYNOTE-021G trials, which is a small sample size phase II clinical trial. Nine treatments for 7,367 untreated NSCLC patients were included for analysis. The results were stable and were similar to main analysis after excluding KEYNOTE-021G. Outcomes of node-splitting analysis indicated that there is no inconsistency exist then we did not conduct NMA in consistency model. Begg's and Egger's test demonstrated no obvious publication bias existed (Figures S7-S18).

Discussion

PD-1/L1 inhibitors are now widely used in solid tumors,

Table 2 Study and demographical characters of included RCTs

Study name	Publication	Male (%)		Age (median)		Non-squamous cell carcinoma (%)		Smoker (%)		ECOG 0 (%)		Asia (%)		Brain metastases (%)	
		Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control	Experiment	Control
KEYNOTE 021G	AACR	22 (37.0)	26 (41.0)	62.5	63.2	60 (100)	63 (100)	45 (75.0)	54 (86.0)	24 (40.0)	29 (46.0)	5 (8.0)	5 (8.0)	9 (15.0)	6 (10.0)
KEYNOTE 024	WCLC	92 (59.7)	95 (62.9)	64.5	66	125 (81.2)	125 (82.8)	149 (96.8)	132 (87.4)	55 (35.7)	53 (35.1)	21 (13.6)	19 (12.6)	18 (11.7)	10 (6.6)
KEYNOTE 407	ESMO	220 (79.1)	235 (83.6)	65	65	0	0	256 (92.1)	262 (93.2)	73 (26.3)	90 (32.0)	54 (19.4)	52 (18.5)	20 (7.2)	24 (8.5)
KEYNOTE 042	Lan Onco	450 (70.6)	452 (71.0)	63	63	394 (61.9)	388 (60.9)	495 (77.7)	497 (78.0)	198 (31.1)	192 (30.1)	185 (29.0)	185 (29.0)	NG	NG
KEYNOTE 189	ASCO	254 (62.0)	109 (52.9)	65	63.5	410 (100)	206 (100)	362 (88.3)	181 (87.9)	186 (45.4)	80 (38.8)	4 (1.0)	6 (2.9)	73 (17.8)	35 (17.0)
CheckMate 026	NEJM	184 (67.9)	148 (54.8)	63	65	205 (75.6)	206 (76.3)	238 (87.8)	237 (87.8)	85 (31.4)	93 (34.4)	30 (11.1)	17 (6.3)	33 (12.2)	36 (13.3)
CheckMate 227	ESMO	130 (73.4)	125 (67.2)	64	64	134 (75.7)	140 (75.3)	147 (83.1)	159 (85.5)	59 (33.3)	57 (30.6)	36 (20.3)	43 (23.1)	NG	NG
	NEJM	393 (67.4)	385 (66.0)	64	64	419 (71.9)	421 (72.2)	497 (85.2)	499 (85.6)	204 (35.0)	191 (32.8)	NG	NG	NG	NG
CAMEL	WCLC	146 (71.2)	149 (72.0)	59	61	205 (100)	207 (100)	NG	NG	48 (23.4)	36 (17.5)	NG	NG	10 (4.9)	6 (2.9)
IMpower 110	ESMO	196 (70.8)	193 (69.7)	NG	NG	192 (69.3)	193 (69.7)	240 (86.6)	242 (87.4)	97 (35.0)	102 (36.8)	45 (16.2)	30 (10.8)	NG	NG
IMpower 130	Lan Onco	266 (59.0)	134 (58.8)	64	65	451 (100)	228 (100)	403 (89.4)	211 (92.5)	189 (42.0)	91 (39.9)	12 (2.7)	3 (1.3)	NG	NG
IMpower 131	WCLC	279 (81.0)	278 (82.0)	65	65	0	0	311 (91.0)	316 (93.0)	115 (34.0)	110 (32.0)	41 (12.0)	37 (11.0)	NG	NG
IMpower 132	ESMO & WCLC	192 (65.8)	192 (67.1)	64	63	292 (100)	286 (100)	255 (87.3)	256 (89.5)	126 (43.2)	114 (40.1)	71 (24.3)	65 (22.7)	NG	NG

RCT, randomized controlled trial; ECOG, Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. NEJM, New England Journal Medicine; ASCO, American Society of Clinical Oncology congress; ESMO, conference of European Society for Medical Oncology congress; WCLC, World conference on lung cancer; Lan Onco, Lancet Oncology; AACR, American Association for Cancer Research; NG, not given.

Table 3 Study and demographical characters of included RCTs

Study name	Publication	PD-L1 expression	PD-L1 test	PD-L1 TPS <1%		PD-L1 TPS 1-49%		PD-L1 TPS >50%	
				Experiment	Control	Experiment	Control	Experiment	Control
KEYNOTE 021G	AACR	Any	IHC 22C3 pharmDx assay	21 (35.0%)	23 (37.0%)	19 (32.0%)	23 (37.0%)	20 (33.0%)	17 (27.0%)
KEYNOTE 024	WCLC	≥50%	IHC 22C3 pharmDx assay	-	-	-	-	154 (100%)	151 (100%)
KEYNOTE 407	ESMO	Any	IHC 22C3 pharmDx assay	95 (34.2%)	99 (35.2%)	103 (37.1%)	104 (37.0%)	73 (26.3%)	73 (26.0%)
KEYNOTE 042	Lan Onco	≥1%	NG	-	-	338 (53.1%)	337 (52.9%)	299 (46.9%)	300 (47.1%)
KEYNOTE 189	ASCO	Any	IHC 22C3 pharmDx assay	127 (31.0%)	63 (30.6%)	128 (31.2%)	58 (28.2%)	132 (32.2%)	70 (34.0%)
CheckMate 026	NEJM	≥1%	IHC 28-8 pharmDx assay	-	-	183 (67.5%)	144 (53.3%)	88 (32.5%)	126 (46.7%)
CheckMate 227	ASCO	<1%	IHC 28-8 pharmDx assay	177 (100%)	186 (100%)	-	-	-	-
CAMEL	NEJM	Any	IHC 28-8 pharmDx assay	187 (32.1%)	186 (31.9%)	191 (32.8%)	205 (35.2%)	205 (35.2%)	192 (32.9%)
IMpower 110	WCLC	Any	NG	49 (24.1%)	69 (34.0%)	108 (52.7%)	97 (46.9%)	29 (14.3%)	20 (9.9%)
IMpower 130	ESMO	≥1%	NG	-	-	170 (61.4%)	179 (64.6%)	107 (38.6%)	98 (35.4%)
IMpower 131	Lan Onco	Any	NG	235 (52.1%)	121 (53.1%)	128 (28.4%)	65 (28.5%)	88 (19.5%)	42 (18.4%)
IMpower 132	WCLC	Any	NG	160 (46.6%)	171 (50.3%)	129 (37.6%)	121 (35.6%)	53 (15.4%)	48 (14.1%)
	ESMO & WCLC	Any	NG	88 (50.0%)	75 (44.6%)	63 (35.8%)	73 (34.5%)	25 (14.2%)	20 (11.9%)

RCT, randomized controlled trial; PD-L1, programmed death ligand 1; TPS, tumor proportion score; NEJM, New England Journal Medicine; ASCO, American Society of Clinical Oncology congress; ESMO, conference of European Society for Medical Oncology congress; WCLC, World conference on lung cancer; Lan Onco, Lancet Oncology; AACR, American Association for Cancer Research.

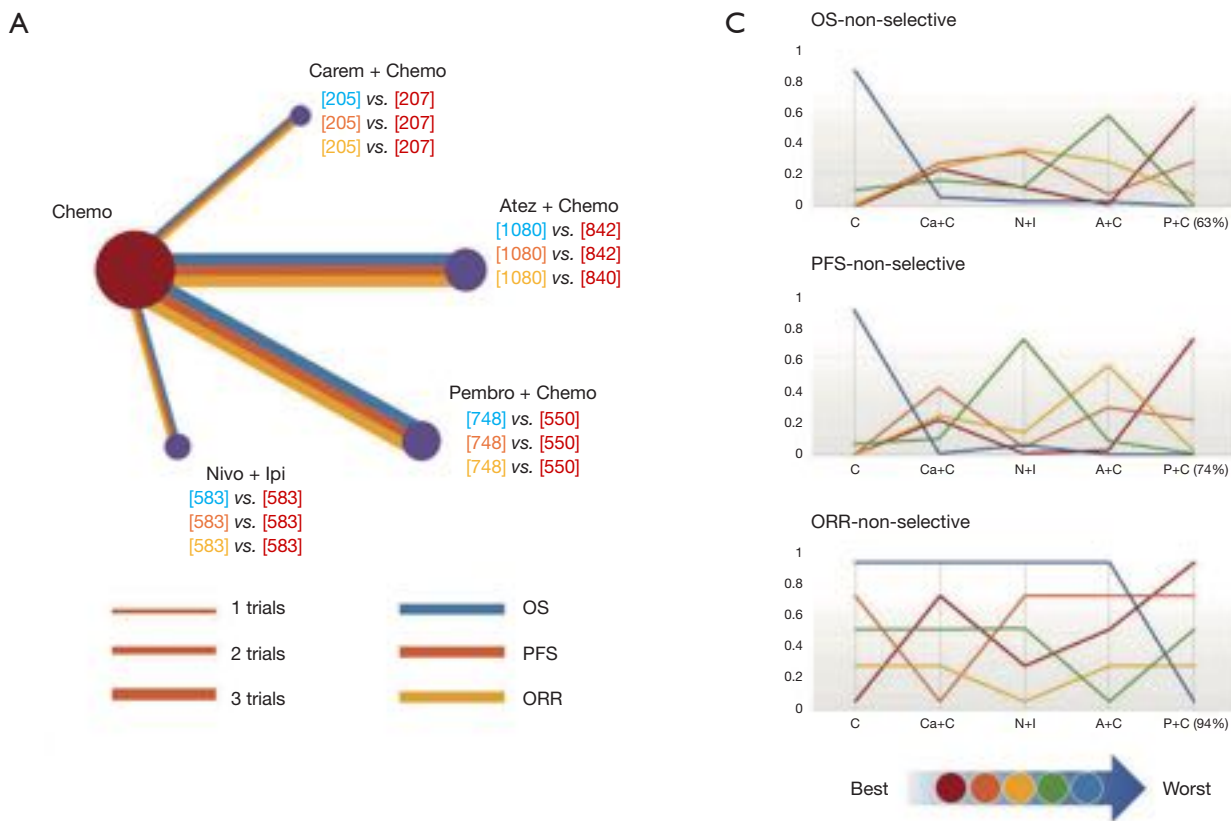


Figure 2 Efficacy for PD-1/L1 inhibitors for PD-L1 non-selective NSCLC patients. (A) Network plot of five treatments on OS, PFS and ORR. The width of lines is proportional to the number of trials. (B) Multiple comparisons for OS, PFS and ORR based on network consistency model (HR <1 or OR >1 indicates better efficacy). (C) Ranking plots based on the comparisons of these five treatments on OS, PFS and ORR. Polylines represent the probabilities of each treatment being first to last. Chemo (C), chemotherapy; Carem + Chemo (Ca + C), caremlizumab plus chemotherapy; Nivo + Ipi (N + I), nivolumab plus ipilimumab; Atez + Chemo (A + C), atezolizumab plus chemotherapy; Pembro + Chemo (P + C), pembrolizumab plus chemotherapy; PD-1/L1, programmed death 1/ligand 1; OS, overall survival; PFS, progression free survival; ORR, objective response rate; NSCLC, non-small cell lung cancer.

Table 4 Single arm meta-analysis for ORR in each treatment in PD-L1 non-selective NSCLC patients

Treatment	ORR	95% CI (lower)	95% CI (upper)
Chemo	0.33	0.31	0.35
Carem + Chemo	0.60	0.53	0.67
Nivo + Ipi	0.33	0.29	0.37
Atez + Chemo	0.49	0.46	0.52
Pembro + Chemo	0.54	0.50	0.58

Chemo, chemotherapy; Carem + Chemo, carelizumab plus chemotherapy; Nivo, nivolumab; Nivo + Ipi, nivolumab plus ipilimumab; Nivo + Chemo, nivolumab plus chemotherapy; Atez, atezolizumab; Atez + Chemo, atezolizumab plus chemotherapy; Pembro, pembrolizumab; Pembro + Chemo, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; ORR, objective response rate; NSCLC, non-small cell lung cancer.

including NSCLC. Meanwhile, some agents are rapidly promoted to first-line treatment. However, systematic comparisons among treatment strategies are lacking. Our research provided evidence to fill this gap and accurate clinical application of PD-1/L1 inhibitors in first line treatment of NSCLC.

Basing on 12 RCTs, the results of this NMA suggested that the combination of pembrolizumab and chemotherapy had potential advantage in terms of OS, PFS, ORR in most sub-populations. Moreover, patients with high PD-L1 expression obtain more advantages, this conclusion was also in accordance with previous analyses (20,21). Besides the combination of pembrolizumab and chemotherapy, our research provided valuable evidence for the effectiveness of other treatment regimens. For instance, according to the OS of PD-L1 negative patients, Bayesian ranking profiles suggested that the combination of nivolumab and ipilimumab was the most possible advantageous therapy to be ranked at first (probability =45%). More studies should be performed to validate and explore the optimal situation to use the doublet immunotherapy agents.

In this research, we found different PD-1/L1 agents had different efficacy in monotherapy and combination therapy. Several possible reasons might attribute to this phenomenon. There are two considerations from the perspective of drugs' mechanism. (I) The different mechanisms between PD-1 and PD-L1 inhibitors. Although both inhibitors have therapeutic effect by blocking the binding of PD-1 to PD-L1, PD-1 inhibitors and PD-L1 inhibitors target different binding sites. Some researches

indicated that PD-L1 inhibitors could produce a stronger immune response than PD-1 inhibitors due to that they could block both PD-L1/PD-1 and PD-L1/B7-1 pathway (22-25). Although PD-1 inhibitors can also bind to PD-L2, the function of PD-L2 in cancer immunosuppression does not seem to be important. Otherwise, PD-1 is expressed on a variety of immune cells, such as monocytes, T cells, B cells, dendritic cells, and tumor-infiltrating lymphocytes. However, PD-L1 is expressed in tumor cells and antigen presenting cells (APCs) (26). Therefore, the number of different cells and the expression of PD-1/PD-L1 may affect the efficacy. (II) The different bio-structure and binding sites among different PD-1/PD-L1 inhibitors. Although PD-1/L1 inhibitors work by binding to PD-1/L1 on tumors or somatic cells, their binding sites and mechanisms are different. For PD-1 inhibitors, nivolumab bound to a completely different area compared with pembrolizumab. The two antibodies bind PD-1 in two different orientations with steric clash. The binding surface of nivolumab on PD-1 is close to that of pembrolizumab, but they do not overlap (24). For PD-L1 inhibitors, atezolizumab and BMS-963559 bind to the upper side close to the N-terminus of PD-L1. In contrast, durvalumab and avelumab bind rather perpendicularly to PD-L1, which means that different drugs will take different forms when they combine to PD-L1 (27). However, some studies revealed that the efficacy of PD-1/L1 inhibitors was drug-independent (28). So, whether the difference of bio-structure and binding sites will play a significant role in the different efficacy of various PD-1/L1 inhibitors is unclear.

There are also another two considerations on design of clinical trials to explain the clinical difference of these immunological agents. (I) Heterogeneity of combination regimens. The included trials were heterogeneous not only in terms of type of checkpoint inhibitors, but also for the combined chemotherapy. For different chemotherapy, we should also consider the differences in synergy with immunotherapy. The binding kinetics of therapeutic antibodies is one of the most important determinants for the ultimate therapeutic function. Different structures in drugs can aid in controlling the surface complementarity of the interface between antibodies and immune checkpoints (28). For chemotherapy, it can stimulate the antigenicity and immunogenicity of malignant cells or increase their susceptibility to immune attacks and may be advantageously combined with immunotherapeutic regimens designed to activate immune effectors or to inhibit immunosuppressive

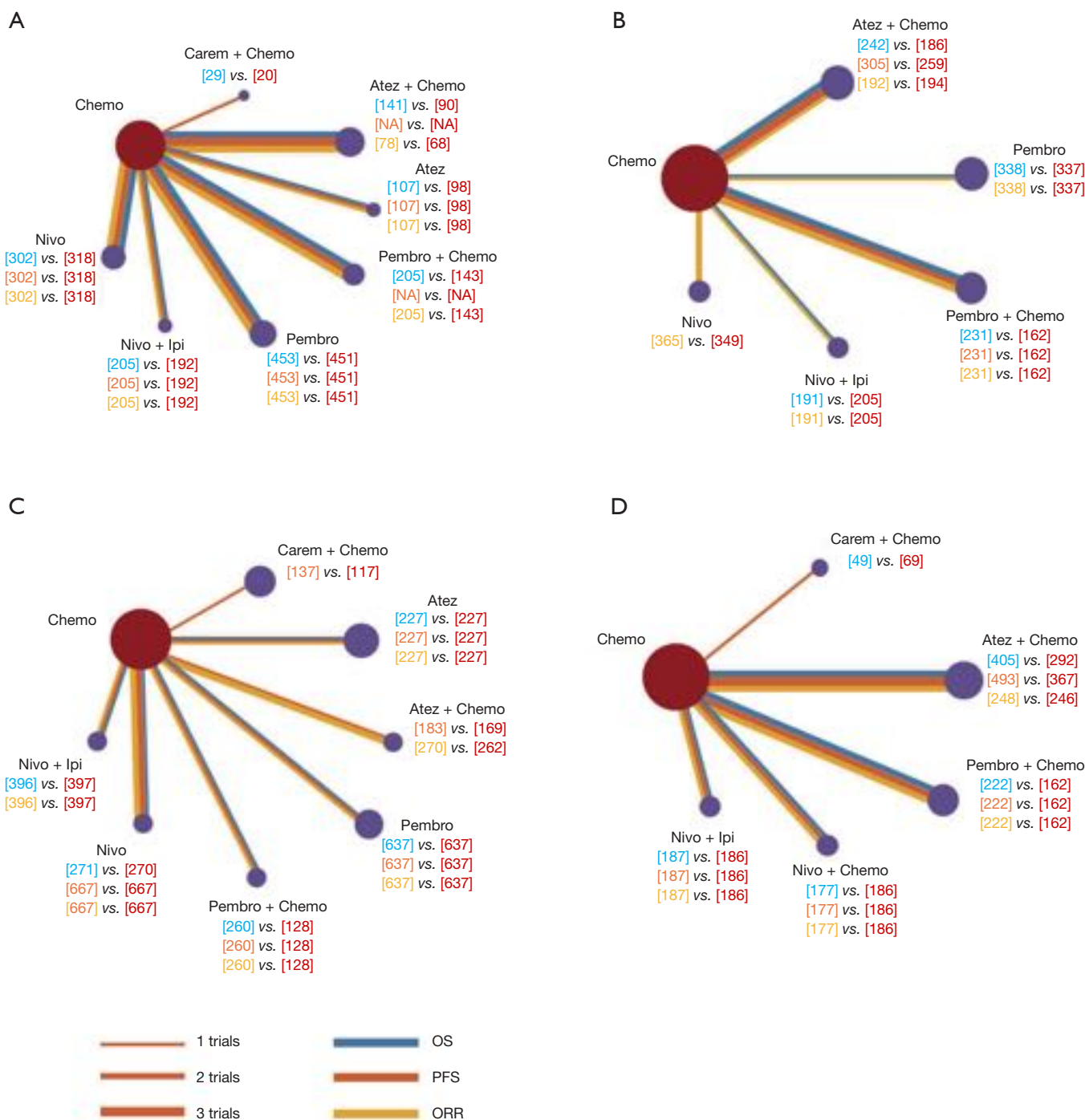


Figure 3 Network plots of reported trials on OS, PFS and ORR in subgroup NSCLC patients according to PD-L1 expression. (A), PD-L1 ≥50% expressed patients (B), PD-L1 1–49% expressed patients (C) PD-L1 positive expressed patients; (D) PD-L1 negative expressed patients. Chemo, chemotherapy; Carem + Chemo, carelizumab plus chemotherapy; Nivo, nivolumab; Nivo + Ipi, nivolumab plus ipilimumab; Nivo + Chemo, nivolumab plus chemotherapy; Atez, atezolizumab; Atez + Chemo, atezolizumab plus chemotherapy; Pembro, pembrolizumab; Pembro + Chemo, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; OS, overall survival; PFS, progression free survival; ORR, objective response rate; NSCLC, non-small cell lung cancer.

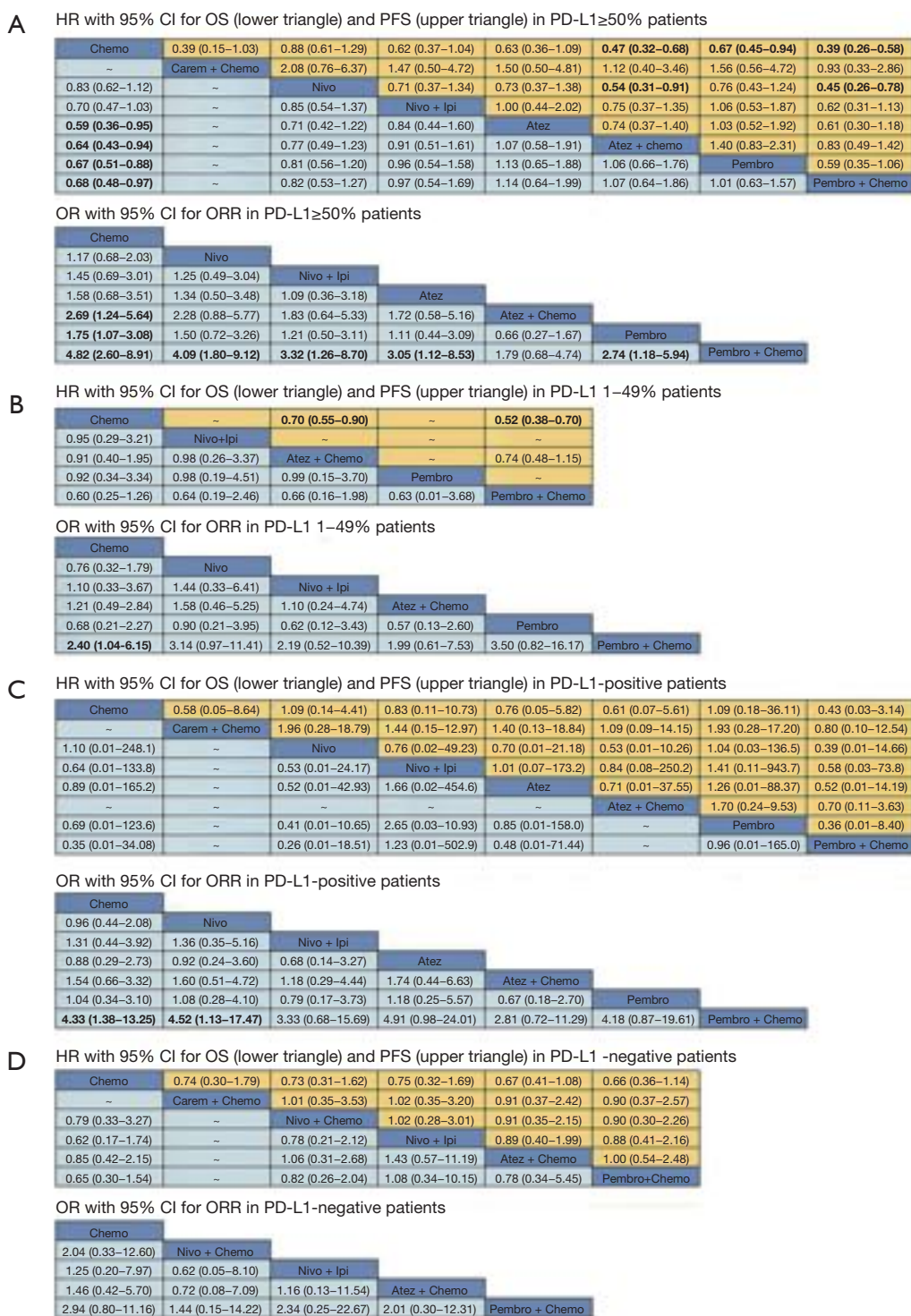


Figure 4 Ranking plots based on the multiple comparisons on OS, PFS and ORR in subgroup NSCLC patients according to PD-L1 expression. Polylines represent the probabilities of each treatment being first to last. C, chemotherapy; Ca + C, caremizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; OS, overall survival; PFS, progression free survival; ORR, objective response rate; NSCLC, non-small cell lung cancer.

Table 5 Single arm meta-analysis for ORR in each treatment according to PD-L1 expression subgroup

Treatment	ORR	95% CI (lower)	95% CI (upper)
PD-L1 ≥50%			
Chemo	0.35	0.32	0.37
Nivo	0.45	0.39	0.51
Nivo + Ipi	0.44	0.38	0.51
Atez	0.38	0.29	0.48
Atez + Chemo	0.64	0.54	0.75
Pembro	0.42	0.38	0.47
Pembro + Chemo	0.63	0.56	0.70
PD-L1 1–49%			
Chemo	0.32	0.29	0.34
Nivo	0.36	0.31	0.41
Nivo + Ipi	0.27	0.20	0.33
Atez + Chemo	0.47	0.40	0.55
Pembro	0.16	0.12	0.20
Pembro + Chemo	0.52	0.46	0.58

Table 5 (continued)

Table 5 (continued)

Treatment	ORR	95% CI (lower)	95% CI (upper)
PD-L1 positive			
Chemo	0.33	0.31	0.35
Nivo	0.40	0.36	0.44
Nivo + Ipi	0.36	0.31	0.41
Atez	0.29	0.24	0.35
Atez + Chemo	0.52	0.46	0.58
Pembro	0.27	0.24	0.31
Pembro + Chemo	0.56	0.50	0.62
PD-L1 negative			
Chemo	0.29	0.26	0.32
Nivo + Chemo	0.38	0.31	0.45
Nivo + Ipi	0.27	0.21	0.34
Atez + Chemo	0.44	0.38	0.50
Pembro + Chemo	0.47	0.41	0.54

Chemo, chemotherapy; Carem + Chemo, carelizumab plus chemotherapy; Nivo, nivolumab; Nivo + Ipi, nivolumab plus ipilimumab; Nivo + Chemo, nivolumab plus chemotherapy; Atez, atezolizumab; Atez + Chemo, atezolizumab plus chemotherapy; Pembro, pembrolizumab; Pembro + Chemo, pembrolizumab plus chemotherapy; ORR, objective response rate; PD-L1, programmed death ligand 1.

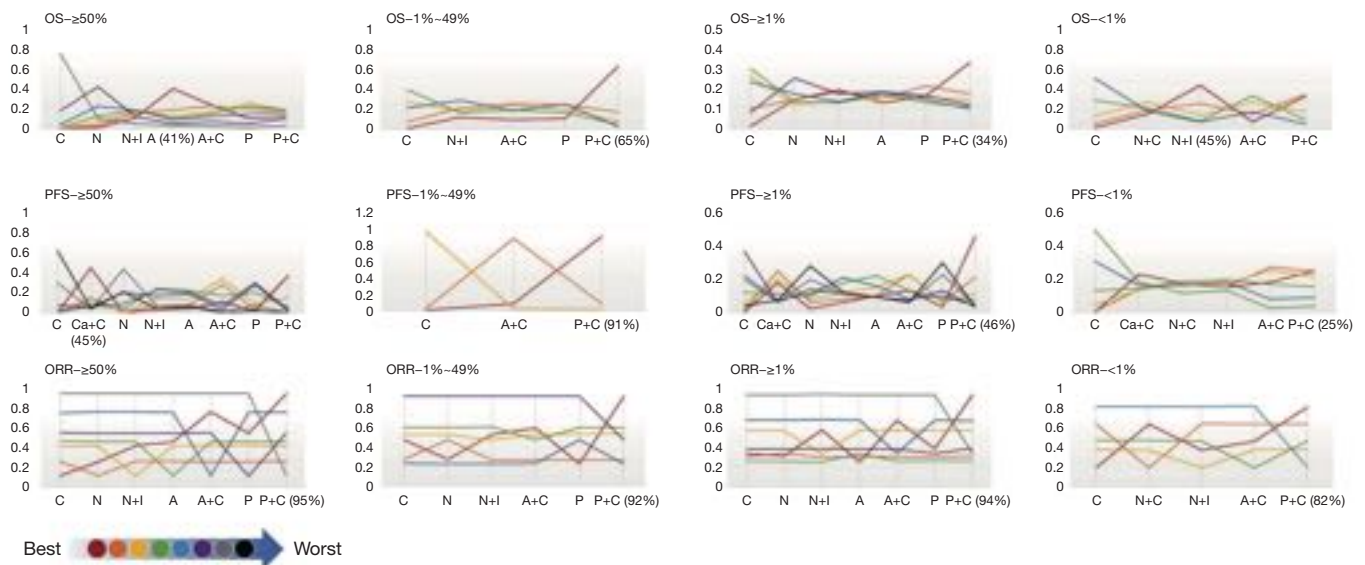


Figure 5 Multiple comparisons on OS, PFS and ORR by network consistency model in subgroup NSCLC patients according to PD-L1 expression (HR <1 or OR >1 indicates better efficacy). (A) PD-L1 ≥50% expressed patients; (B) PD-L1 1–49% expressed patients; (C) PD-L1 positive expressed patients; (D) PD-L1 negative expressed patients. Chemo, chemotherapy; Carem + Chemo, carelizumab plus chemotherapy; Nivo, nivolumab; Nivo + Ipi, nivolumab plus ipilimumab; Nivo + Chemo, nivolumab plus chemotherapy; Atez, atezolizumab; Atez + Chemo, atezolizumab plus chemotherapy; Pembro, pembrolizumab; Pembro + Chemo, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; OS, overall survival; PFS, progression free survival; ORR, objective response rate; NSCLC, non-small cell lung cancer.

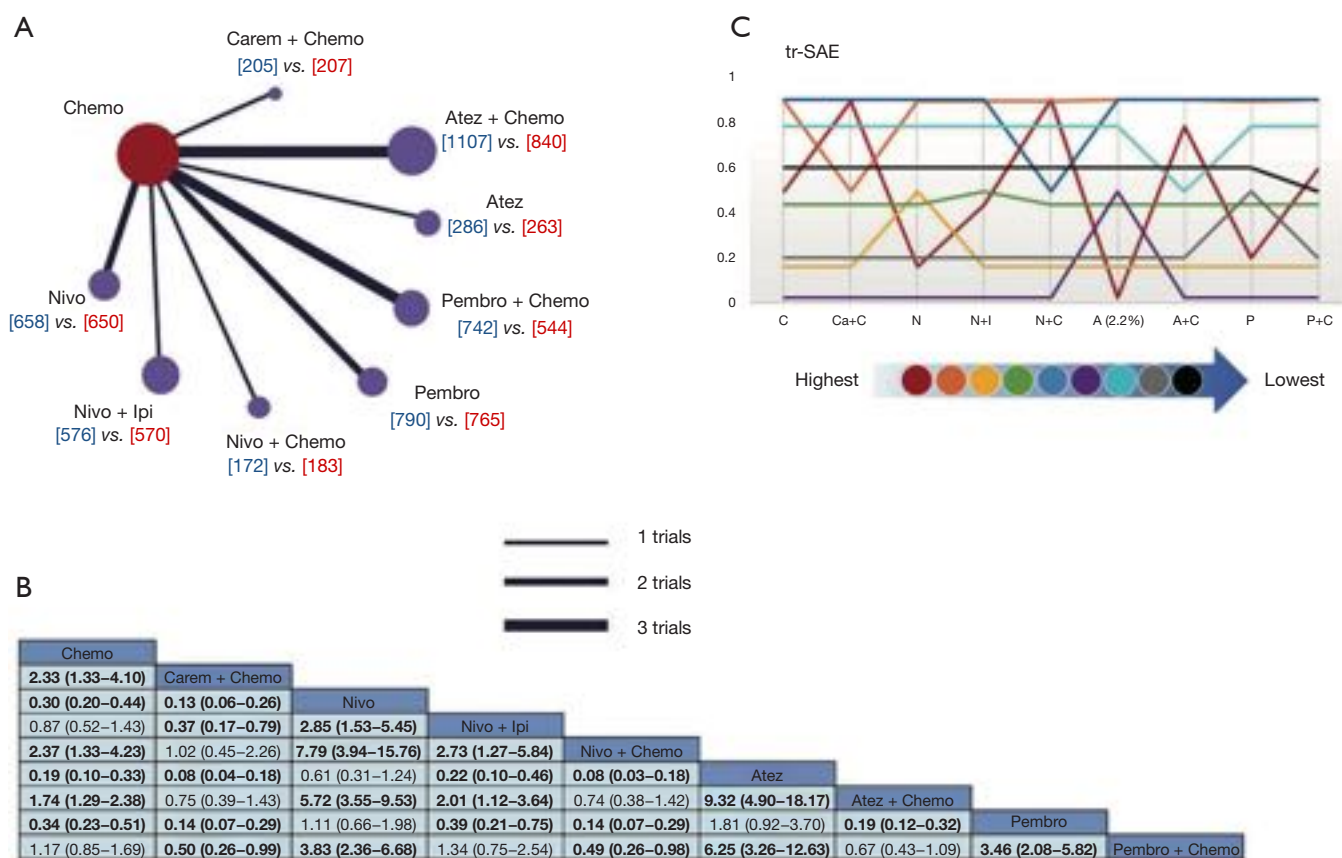


Figure 6 Safety for PD-1/L1 inhibitors for NSCLC patients. (A) Network plot of nine treatments on tr-SAE in all included studies. The width of lines is proportional to the number of trials. (B) Multiple comparison for tr-SAE based on network consistency model (OR >1 indicates higher incidence rate of tr-SAE). (C) Ranking plot based on the comparisons of these nine treatments on tr-SAE. Polylines represent the probabilities of each treatment causing tr-SAE. Chemo (C), chemotherapy; Care + Chemo (Ca + C), carelizumab plus chemotherapy; Nivo (N), nivolumab; Nivo + Ipi (N + I), nivolumab plus ipilimumab; Nivo + Chemo (N + C), nivolumab plus chemotherapy; Atez (A), atezolizumab; Atez + Chemo (A + C), atezolizumab plus chemotherapy; Pembro (P), pembrolizumab; Pembro + Chemo (P + C), pembrolizumab plus chemotherapy; tr-SAE, treatment related adverse event (grade 3 and higher); PD-1/L1, programmed death 1/ligand 1; NSCLC, non-small cell lung cancer.

mechanisms. However, not all chemotherapy regimens have the same effect which will cause different efficacy among various combination therapy regimens (29). (II) The difference of characteristics of eligible patients in each RCT. The clinical characteristics of eligible patients were different, in terms of smoking history, region, the proportion of different tumor histology, differences in PD-L1 assays, scoring and cutoff points employed in trials conducted by different study sponsors, and the impact of these distinctions cannot be ignored.

We acknowledged several limitations in our research. First, subgroup population only based on the PD-L1 expression may still lack the accuracy. Some current studies

pointed out that the prediction of PD-L1 expression on the efficacy of PD-1/L1 inhibitors is not applicable to all types of patients in NSCLC (30,31). Second, we used high-graded adverse events to assess toxicity generally instead of overall adverse events such as low-grade neutrophil count, febrile neutropenia and so on. Therefore, although the incidence of high-level side effects is reduced, detailed side effects may not be reduced but increased for some therapy regimens. Third, all comparisons between therapies in our research are indirect, so more direct comparison data may be needed to support our conclusions. Lastly, some trials are still in progress and complete data cannot be included to participate in the full analysis. Therefore, more clinical trial

Table 6 Single arm meta-analysis for tr-SAE rate

Treatment	tr-SAE	95% CI (lower)	95% CI (upper)
Chemo	0.47	0.45	0.48
Carem + Chemo	0.66	0.60	0.73
Nivo	0.19	0.16	0.22
Nivo + Ipi	0.33	0.29	0.37
Nivo + Chemo	0.56	0.48	0.63
Atez	0.13	0.09	0.17
Atez + Chemo	0.68	0.65	0.71
Pembro	0.20	0.18	0.23
Pembro + Chemo	0.66	0.63	0.69

Chemo, chemotherapy; Carem + Chemo, carelizumab plus chemotherapy; Nivo, nivolumab; Nivo + Ipi, nivolumab plus ipilimumab; Nivo + Chemo, nivolumab plus chemotherapy; Atez, atezolizumab; Atez + Chemo, atezolizumab plus chemotherapy; Pembro, pembrolizumab; Pembro + Chemo, pembrolizumab plus chemotherapy; tr-SAE, treatment related adverse event (grade 3 and higher).

results are needed to support our continued research.

Conclusions

These results indicated that pembrolizumab plus chemotherapy might be associated with the best therapeutic efficacy in first-line treatment for major population of NSCLC patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form. The authors have no conflicts of interest to declare.

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.

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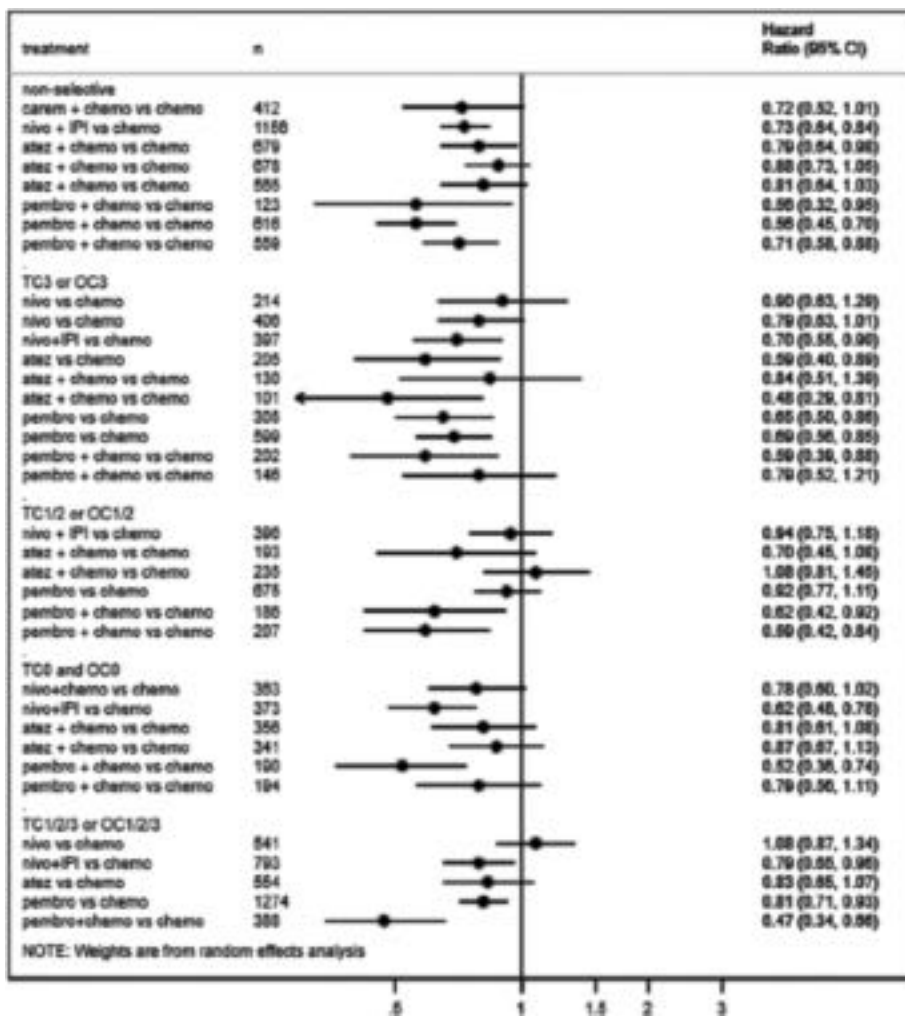
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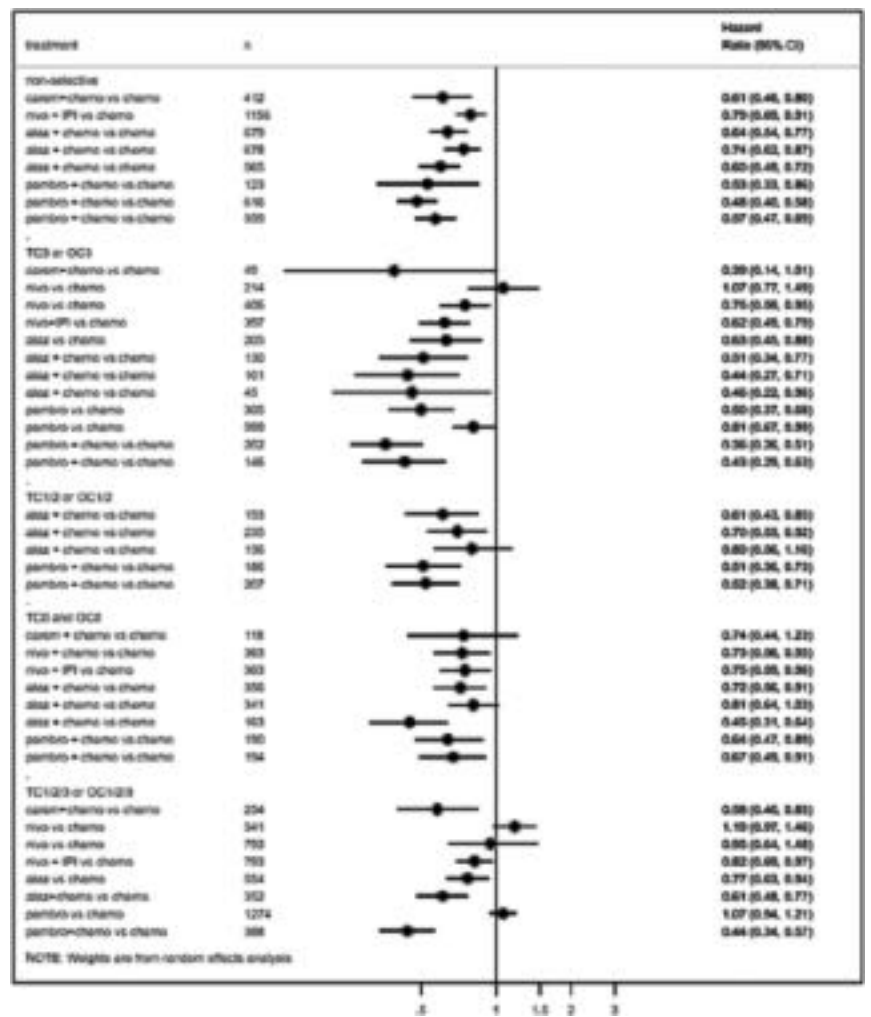
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	Random sequence generation (selection bias)								
	Allocation concealment (selection bias)								
	Blinding of participants and personnel (performance bias)								
	Blinding of outcome assessment (detection bias)								
	Incomplete outcome data (attrition bias)								
	Selective reporting (reporting bias)								
	Other bias								

Figure S1 The bias assessment of eligible trials.

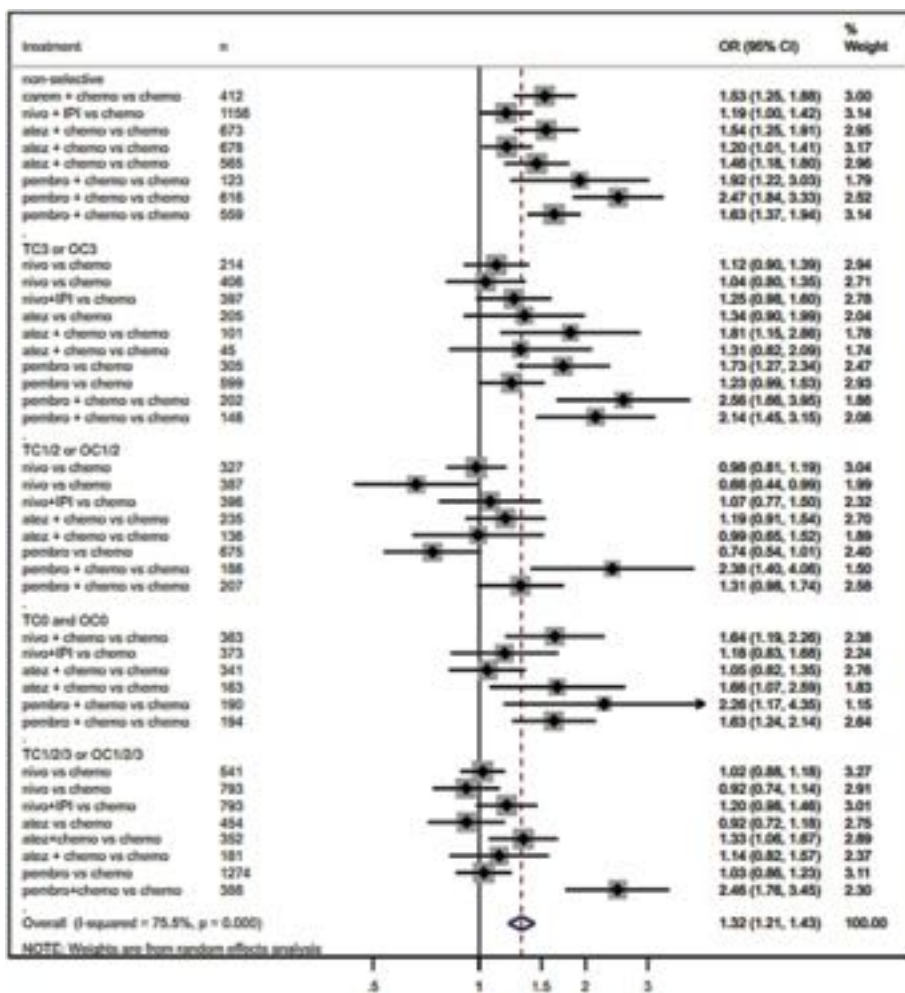
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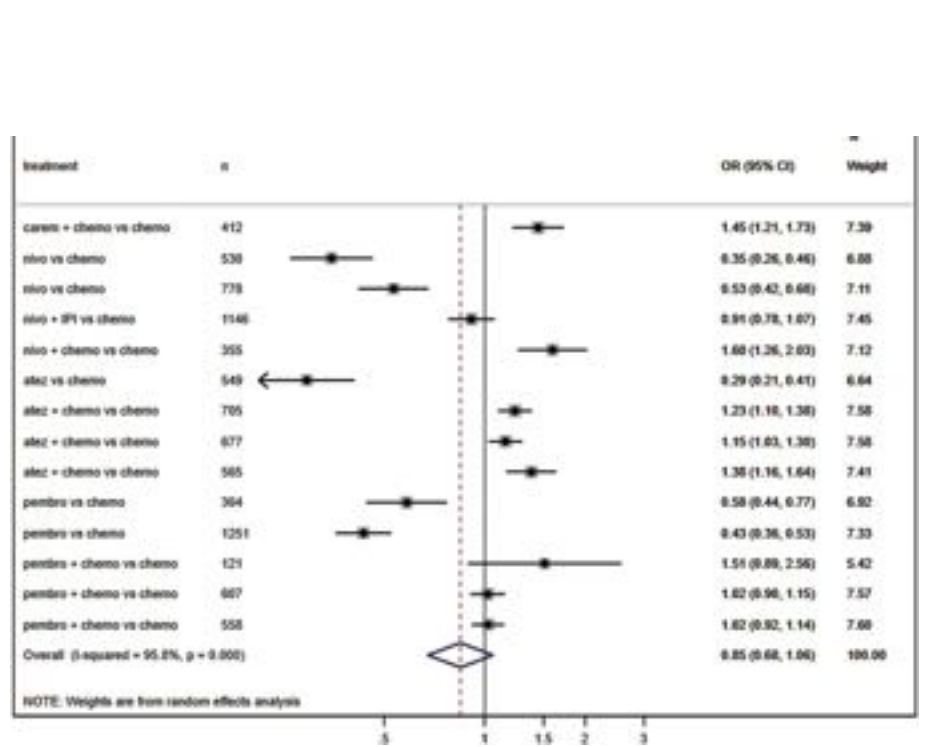


Figure S2 Forest plot of (A) OS, (B) PFS, (C) ORR and (D) tr-SAE meta-estimates by PD-L1 expression level. Chemo, chemotherapy; Carem + Chemo, carelizumab plus chemotherapy; Nivo, nivolumab. Nivo + Ipi, nivolumab plus ipilimumab; Nivo + Chemo, nivolumab plus chemotherapy; Atez, atezolizumab; Atez + Chemo, atezolizumab plus chemotherapy; Pembro, pembrolizumab; Pembro + Chemo, pembrolizumab plus chemotherapy; TC3 or OC3, PD-L1 expression level $\geq 50\%$; TC1/2 or OC1/2, PD-L1 expression level 1–49%; TC0 and OC0, PD-L1-negative; TC1/2/3 or OC1/2/3, PD-L1-positive. PD-L1, programmed death ligand 1; OS, overall survival; PFS, progression free survival; ORR, objective response rate; tr-SAE, treatment-related severe adverse event.

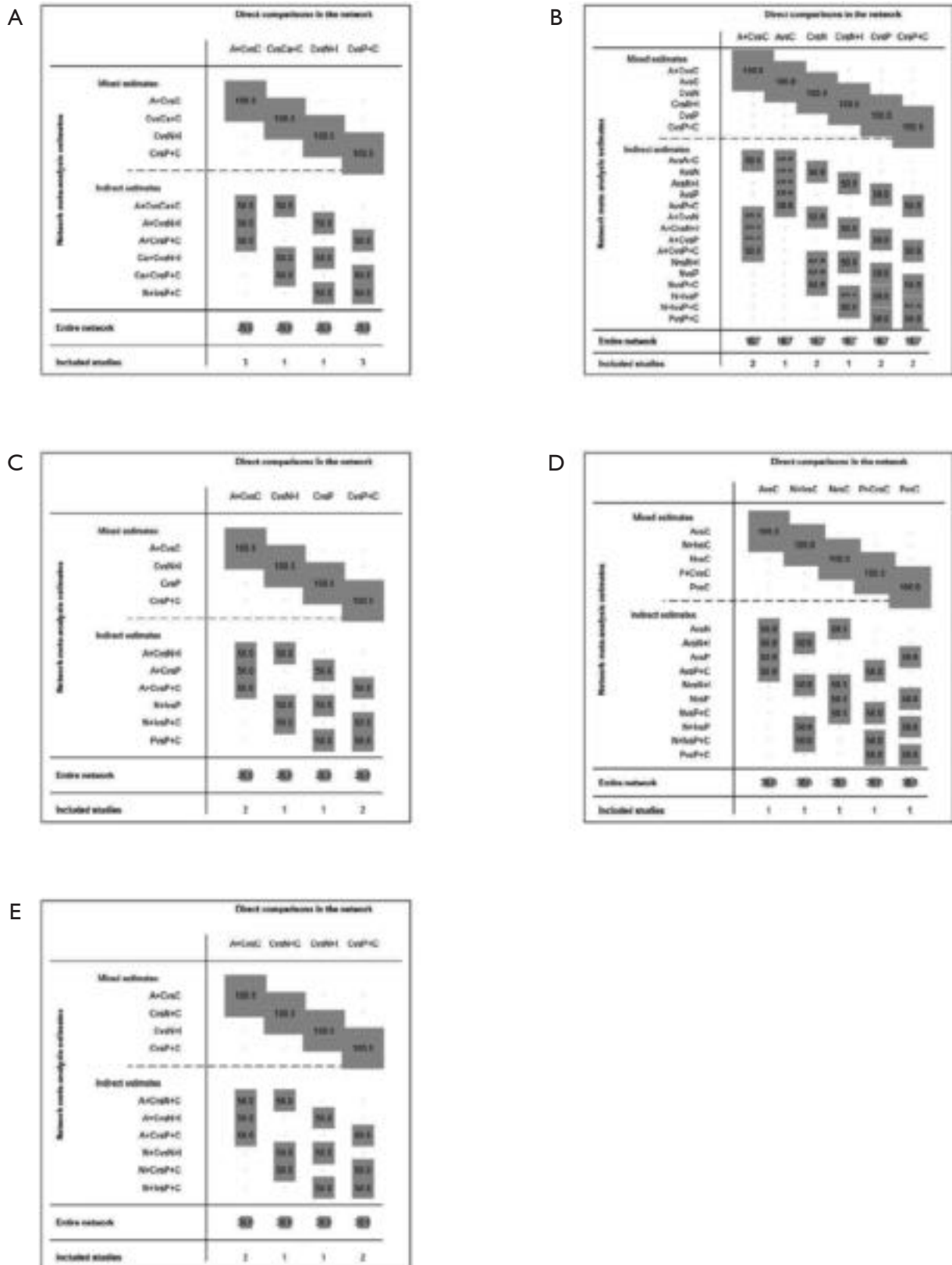


Figure S3 Contribution plots on OS for (A) PD-L1 non-selective, (B) PD-L1 expression 50%, (C) 1–49%, (D) PD-L1 positive and (E) negative patients in NSCLC network. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. C, chemotherapy; Ca + C, caremlizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy; OS, overall survival; PD-L1, programmed death ligand 1; NSCLC, non-small cell lung cancer.

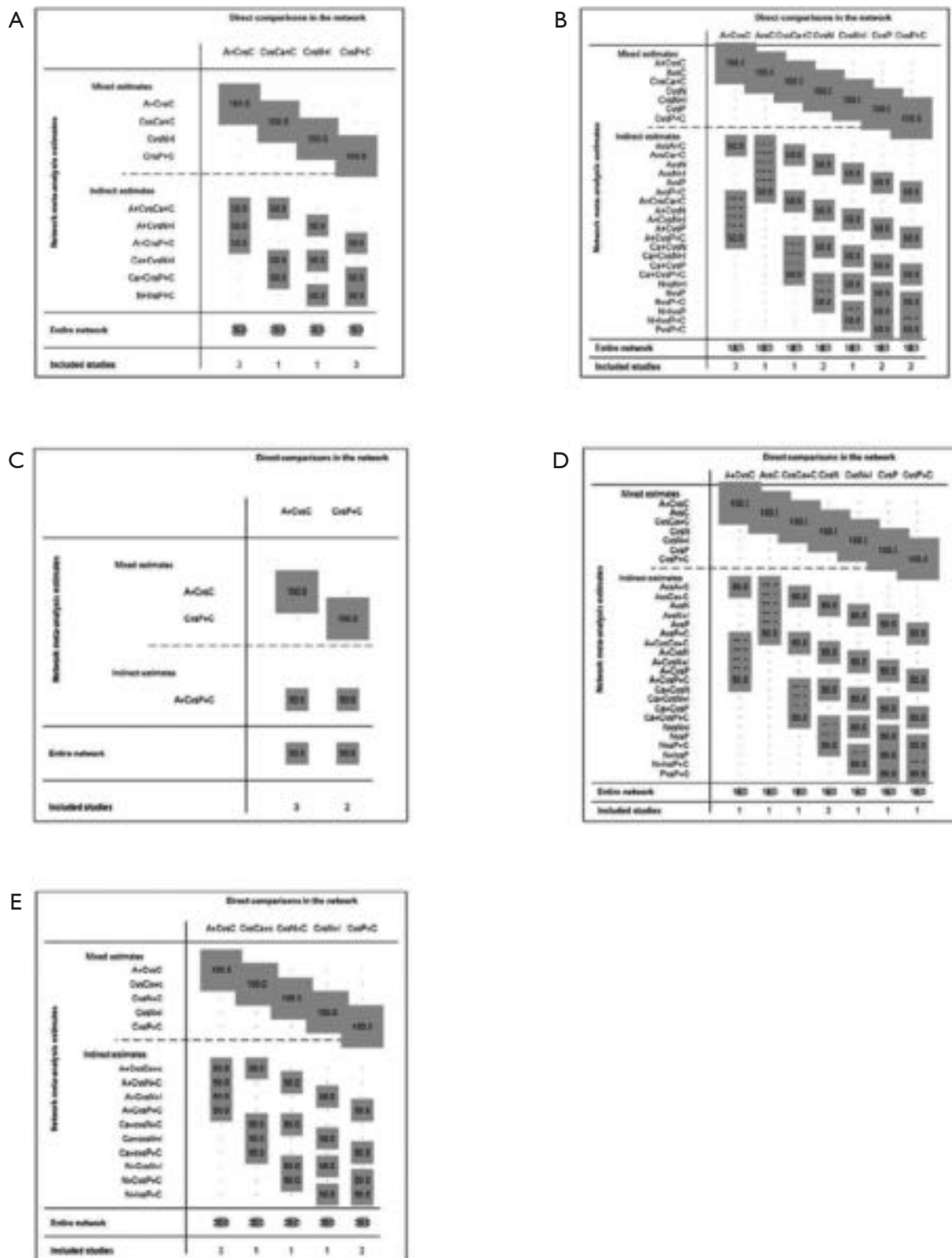


Figure S4 Contribution plots on PFS for (A) PD-L1 non-selective, (B) PD-L1 expression 50%, (C) 1–49%, (D) PD-L1 positive and (E) negative patients in NSCLC network. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. C, chemotherapy; Ca + C, caremizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy. PFS, progression free survival; PD-L1, programmed death ligand 1; NSCLC, non-small cell lung cancer.

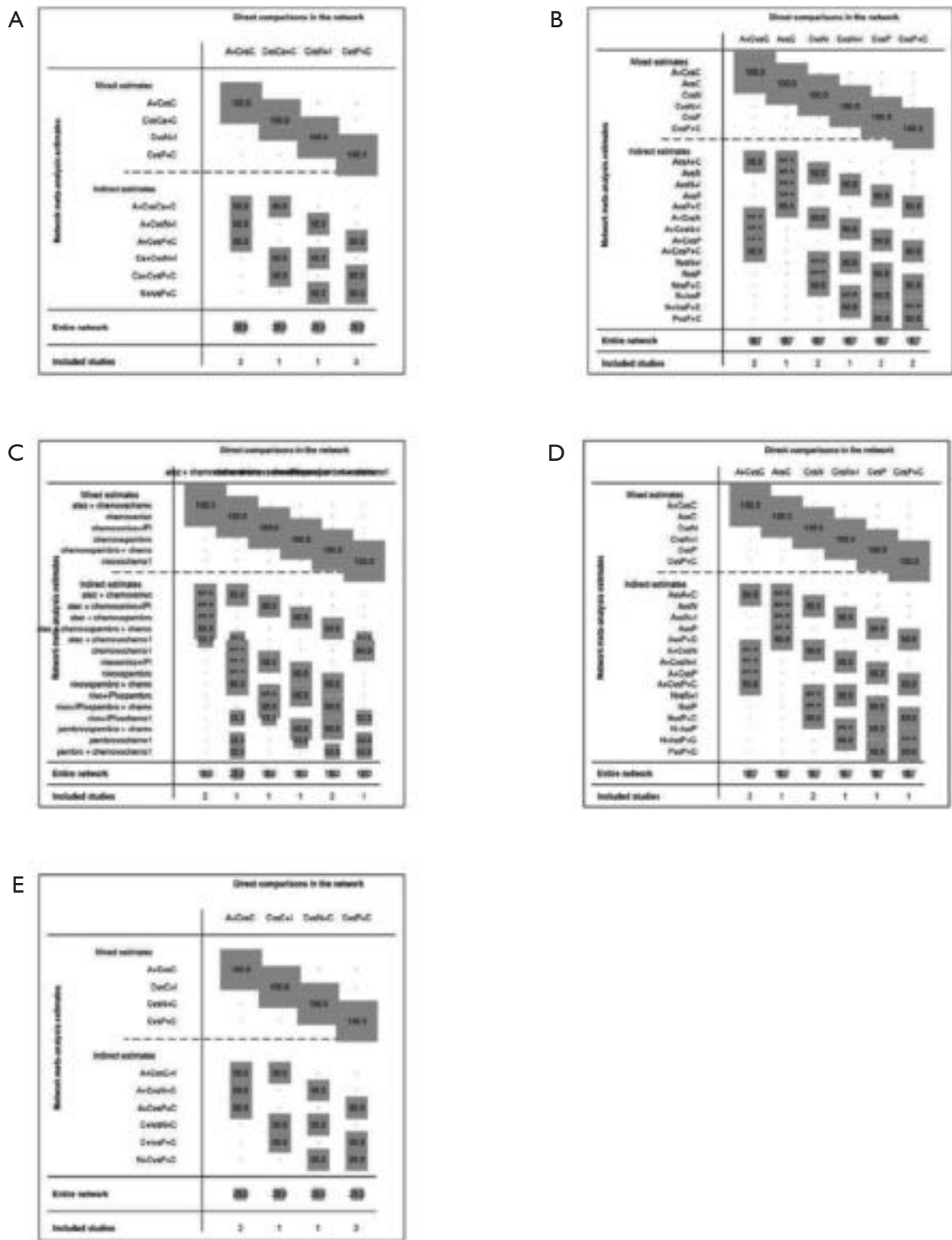


Figure S5 Contribution plots on ORR for (A) PD-L1 non-selective, (B) PD-L1 expression 50%, (C) 1–49%, (D) PD-L1 positive and (E) negative patients in NSCLC network. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. C, chemotherapy; Ca + C, caremizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy. ORR, objective response rate; PD-L1, programmed death ligand 1; NSCLC, non-small cell lung cancer.

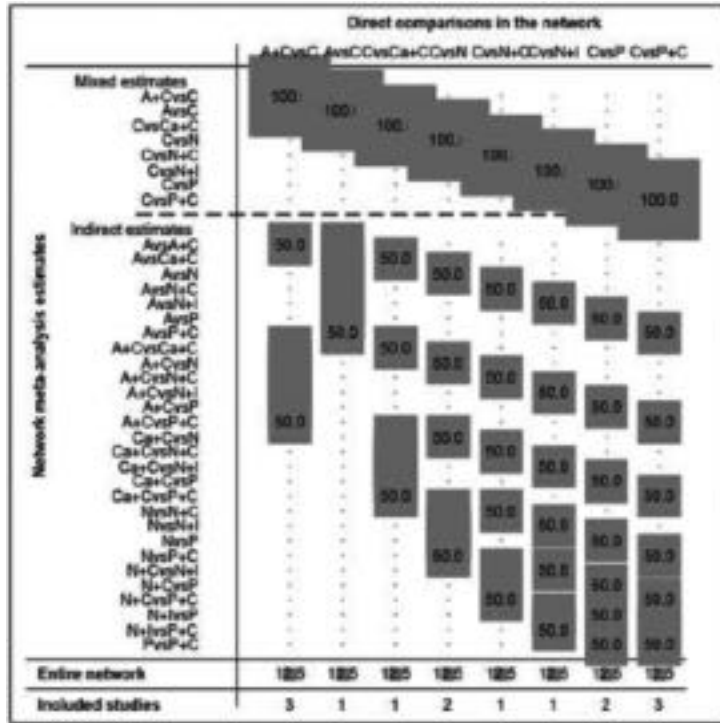


Figure S6 Contribution plots on tr-SAE for PD-L1 non-selective. The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages. C, chemotherapy; Ca + C, caremlizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy. tr-SAE, treatment related severe adverse events (grade 3 or higher); PD-L1, programmed death ligand 1; NSCLC, non-small cell lung cancer.

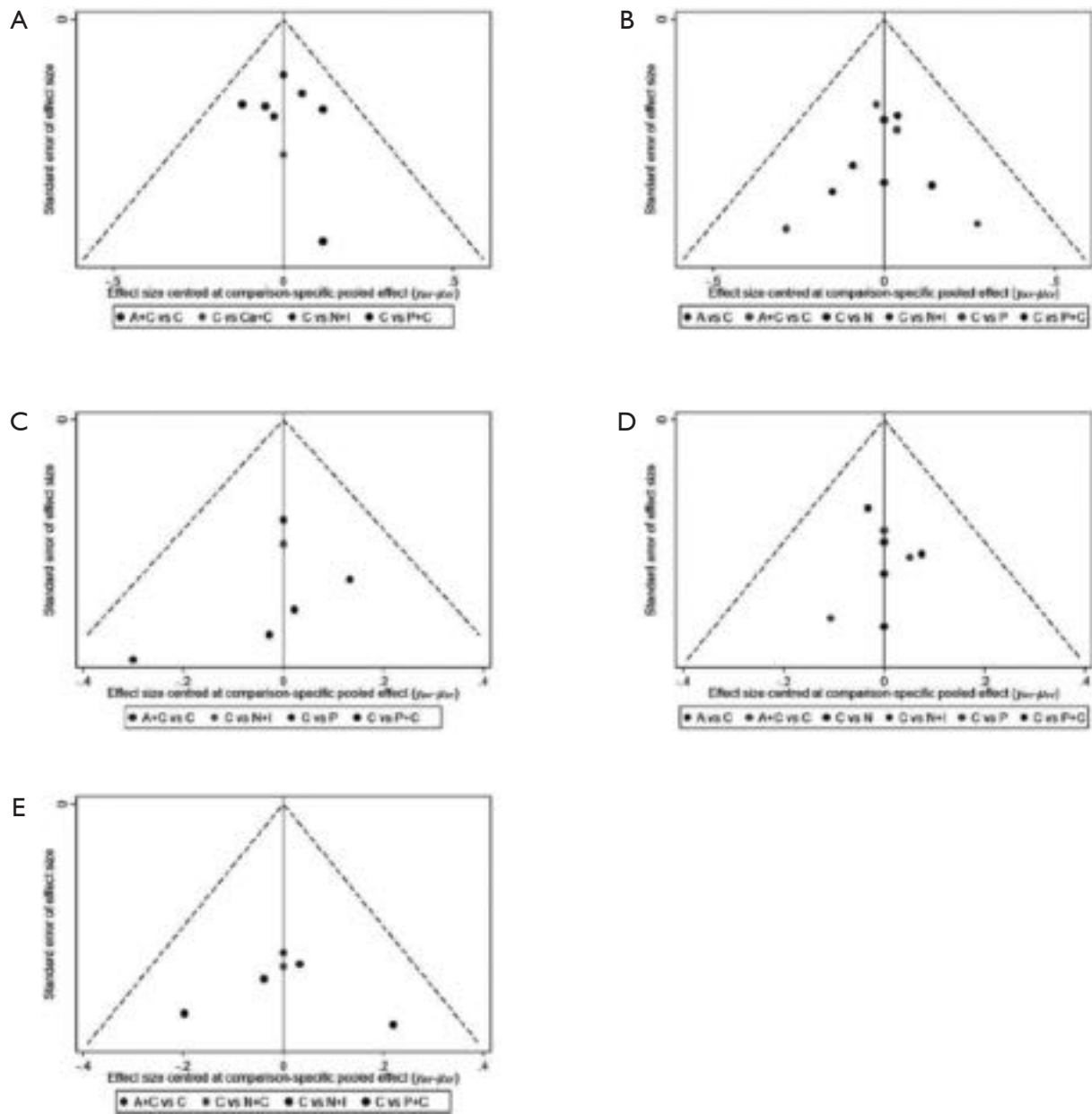


Figure S7 Funnel plots to detect the publication bias of eligible trials on OS by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1–49%, (D) PD-L1-positive and (E) PD-L1-negative. C, chemotherapy; Ca + C, caremlizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; OS, overall survival.

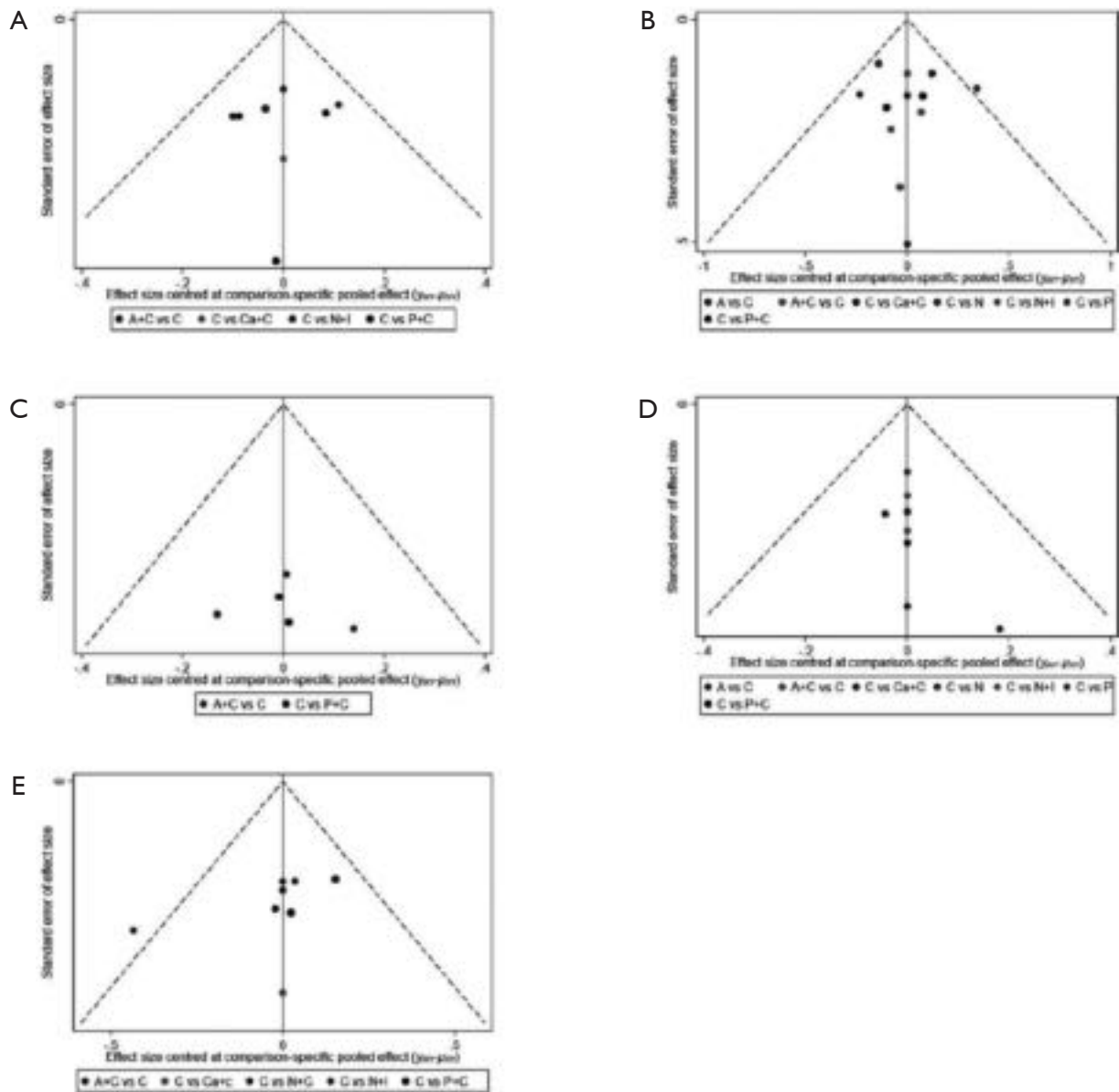


Figure S8 Funnel plots to detect the publication bias of eligible trials on PFS by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1-49%, (D) PD-L1-positive and (E) PD-L1-negative. C, chemotherapy; Ca + C, carelizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1.

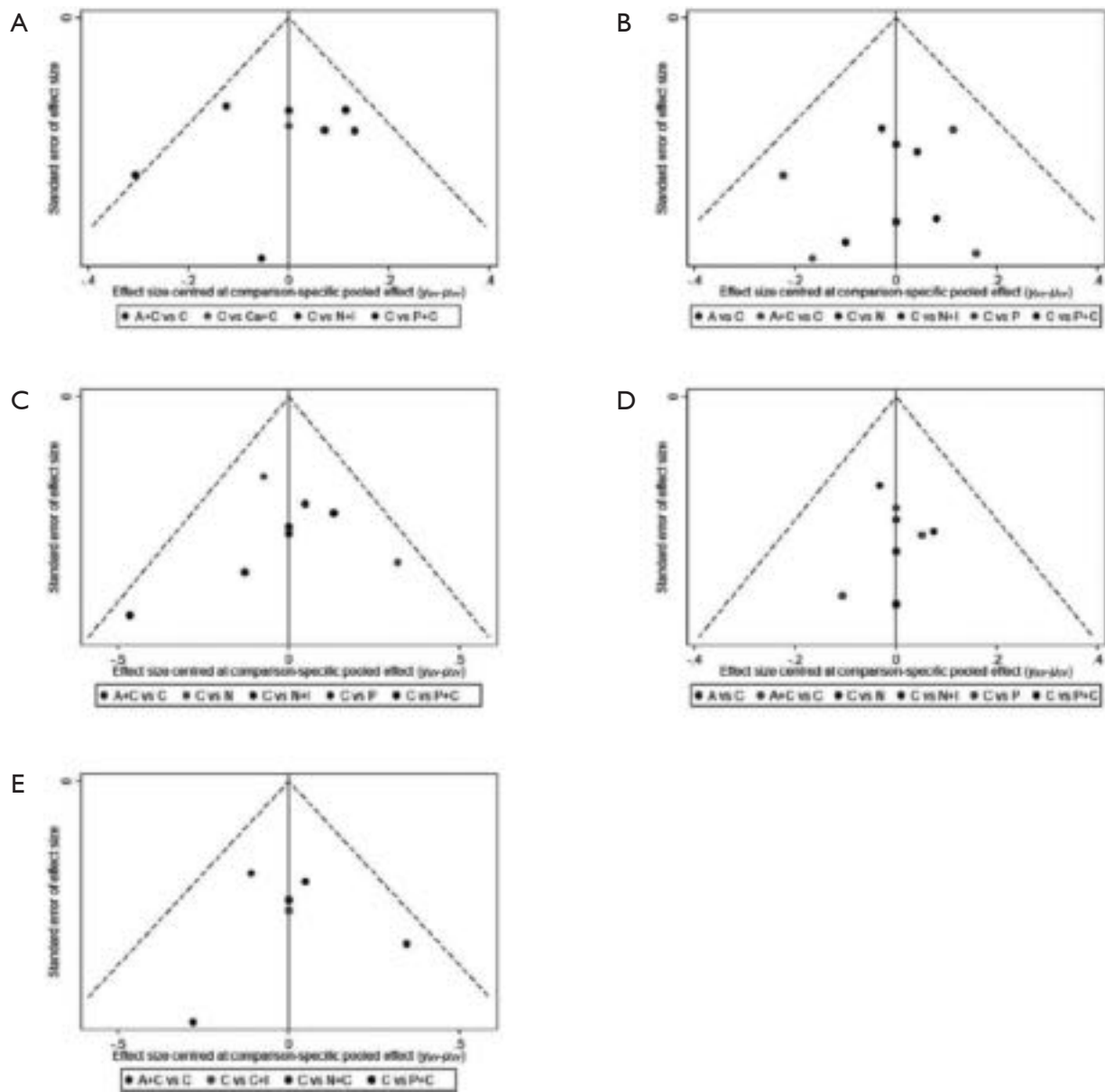


Figure S9 Funnel plots to detect the publication bias of eligible trials on ORR by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1–49%, (D) PD-L1-positive and (E) PD-L1-negative. C, chemotherapy; Ca + C, carelizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; ORR, objective response rate.

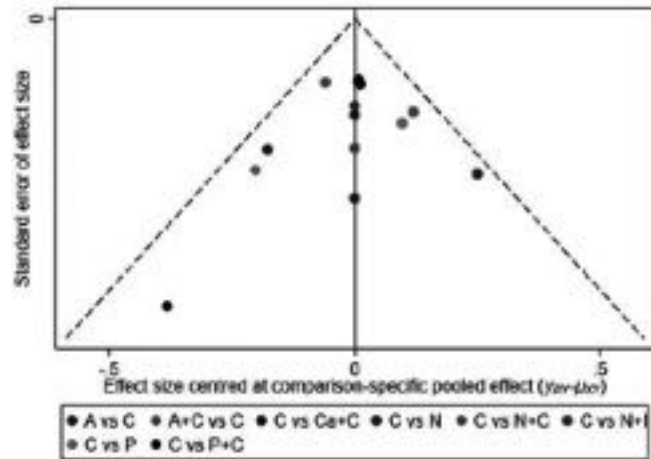


Figure S10 Funnel plots to detect the publication bias of eligible trials on tr-SAE by PD-L1 expression level. C, chemotherapy; Ca + C, carelizumab plus chemotherapy; N, nivolumab; N + I, nivolumab plus ipilimumab; N + C, nivolumab plus chemotherapy; A, atezolizumab; A + C, atezolizumab plus chemotherapy; P, pembrolizumab; P + C, pembrolizumab plus chemotherapy; PD-L1, programmed death ligand 1; tr-SAE, treatment-related severe adverse event.

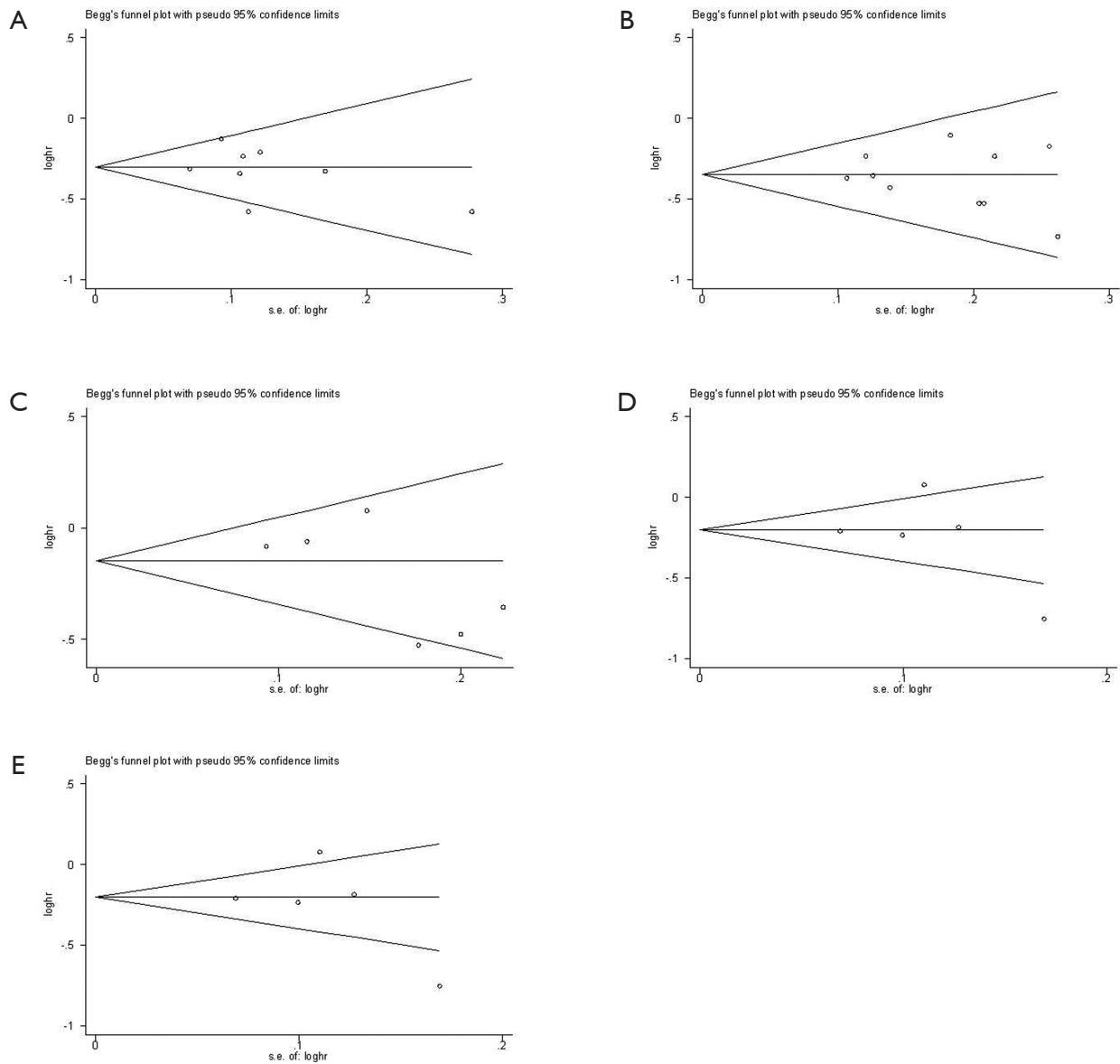


Figure S11 Begg's funnel plots to detect the publication bias of eligible trials on OS by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1–49%, (D) PD-L1-positive and (E) PD-L1-negative. PD-L1, programmed death ligand 1; OS, overall survival.

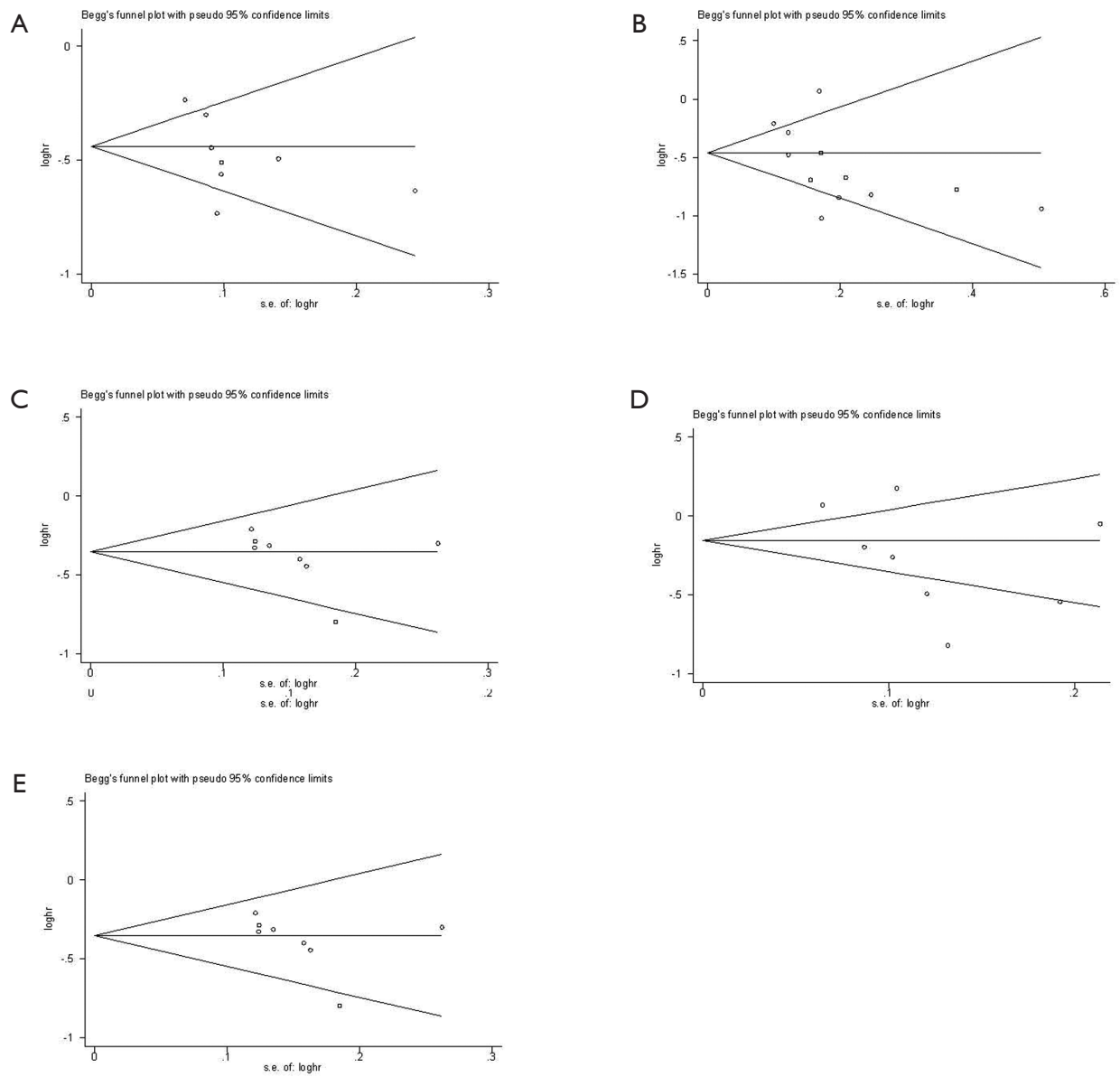


Figure S12 Begg's funnel plots to detect the publication bias of eligible trials on PFS by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1–49%, (D) PD-L1-positive and (E) PD-L1-negative. PD-L1, programmed death ligand 1; PFS, progression free survival.

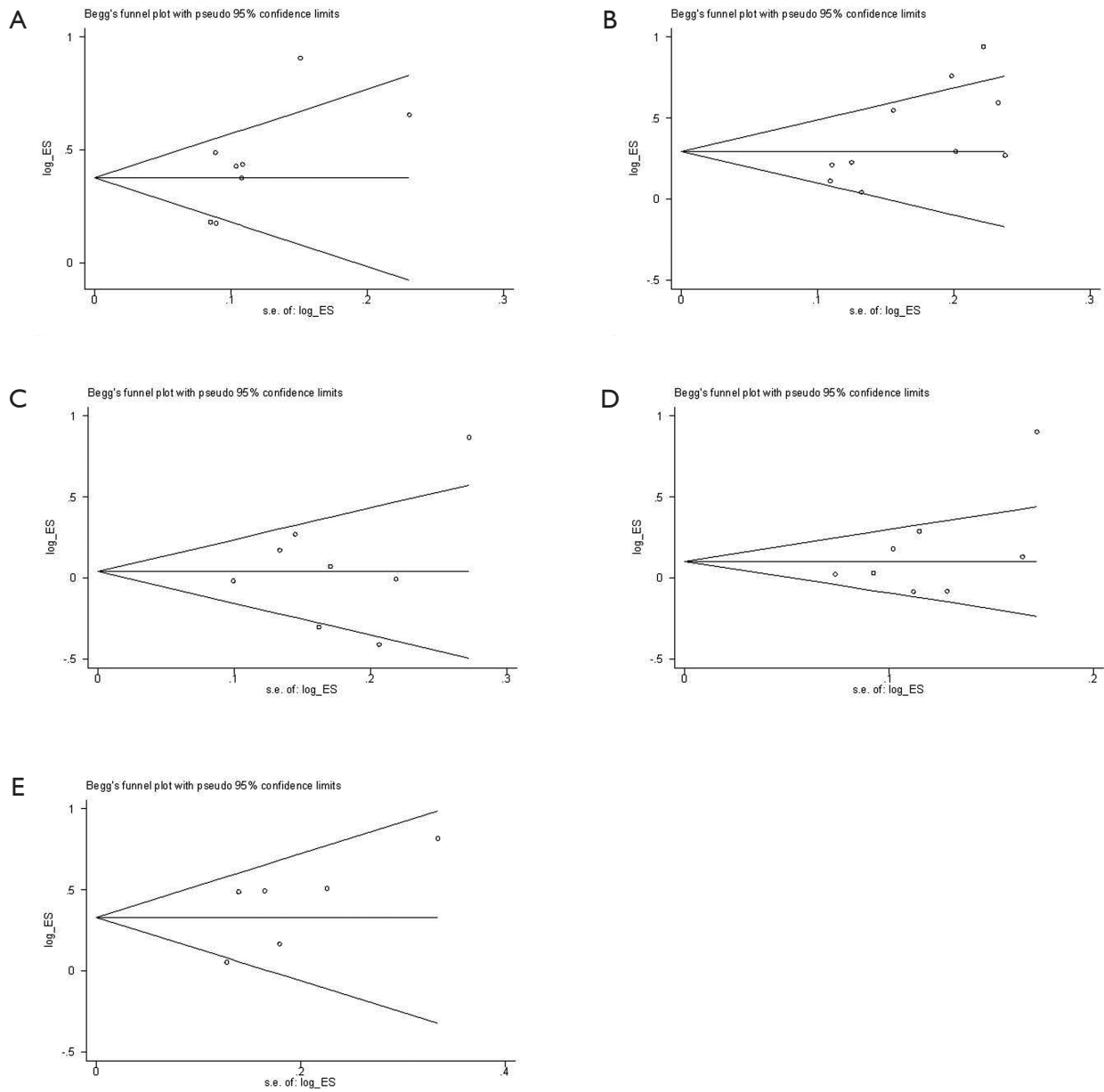


Figure S13 Begg's funnel plots to detect the publication bias of eligible trials on ORR by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1-49%, (D) PD-L1-positive and (E) PD-L1-negative. PD-L1, programmed death ligand 1; ORR, objective response rate.

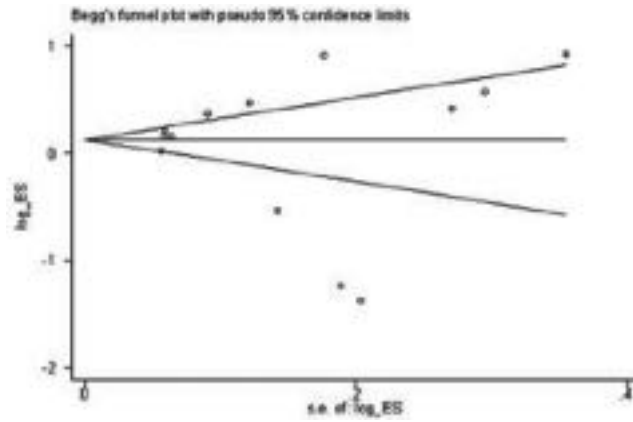


Figure S14 Begg's funnel plots to detect the publication bias of eligible trials on tr-SAE for overall NSCLC patients. tr-SAE, treatment-related severe adverse event; NSCLC, non-small cell lung cancer.

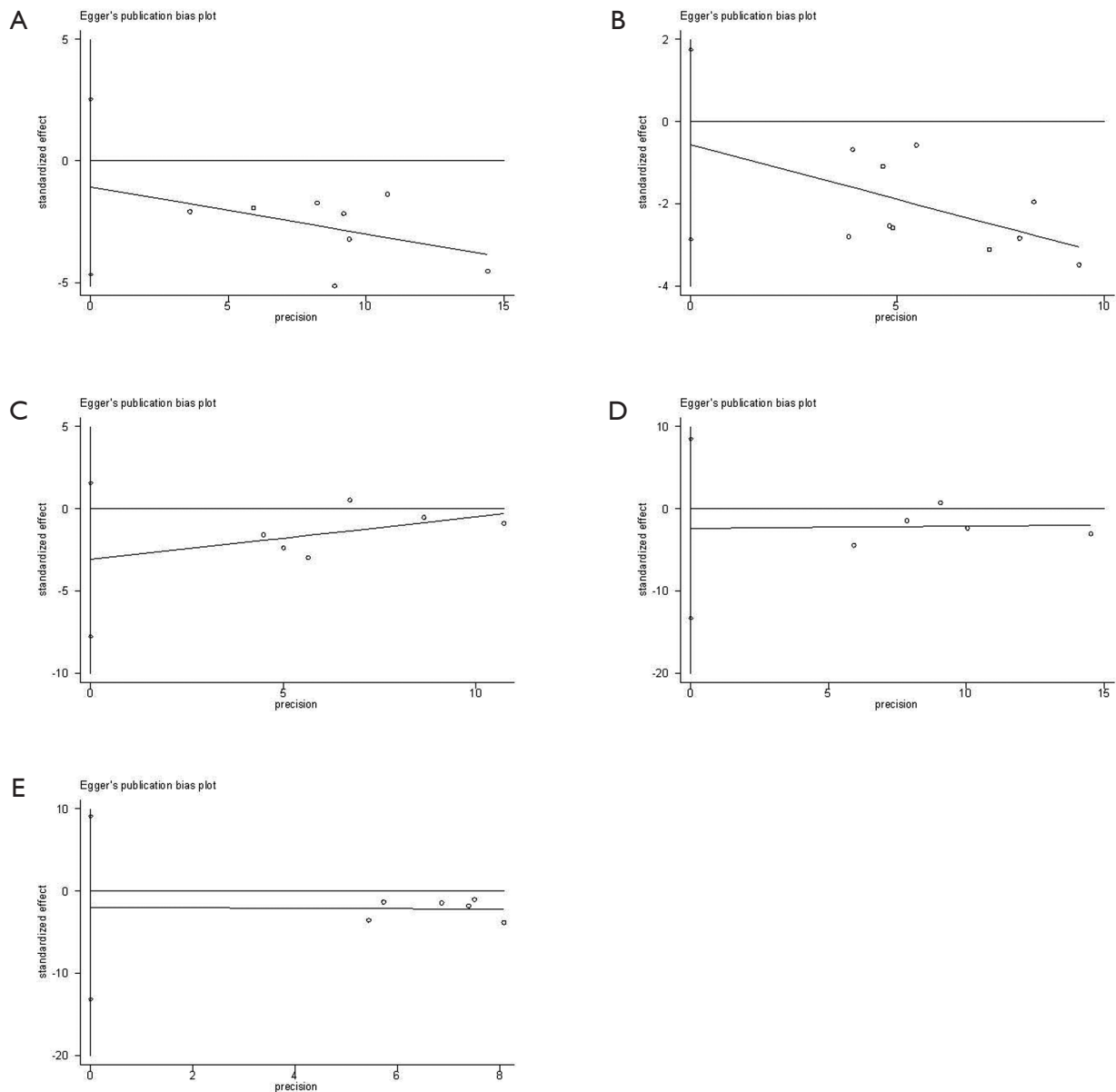


Figure S15 Egger's plots to detect the publication bias of eligible trials on OS by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1–49%, (D) PD-L1-positive and (E) PD-L1-negative. PD-L1, programmed death ligand 1; OS, overall survival.

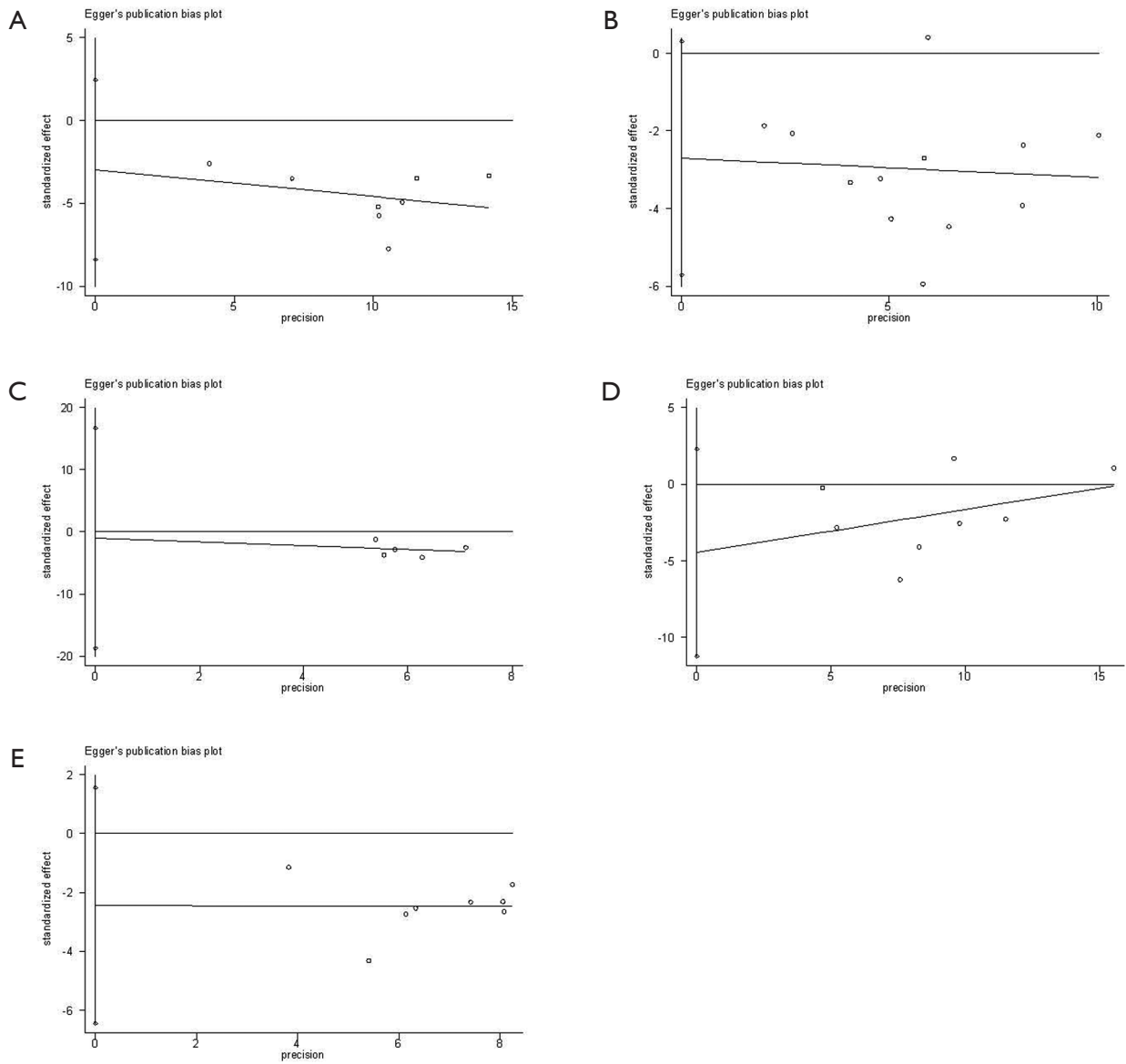


Figure S16 Egger's plots to detect the publication bias of eligible trials on PFS by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1–49%, (D) PD-L1-positive and (E) PD-L1-negative. PD-L1, programmed death ligand 1; PFS, progression free survival.

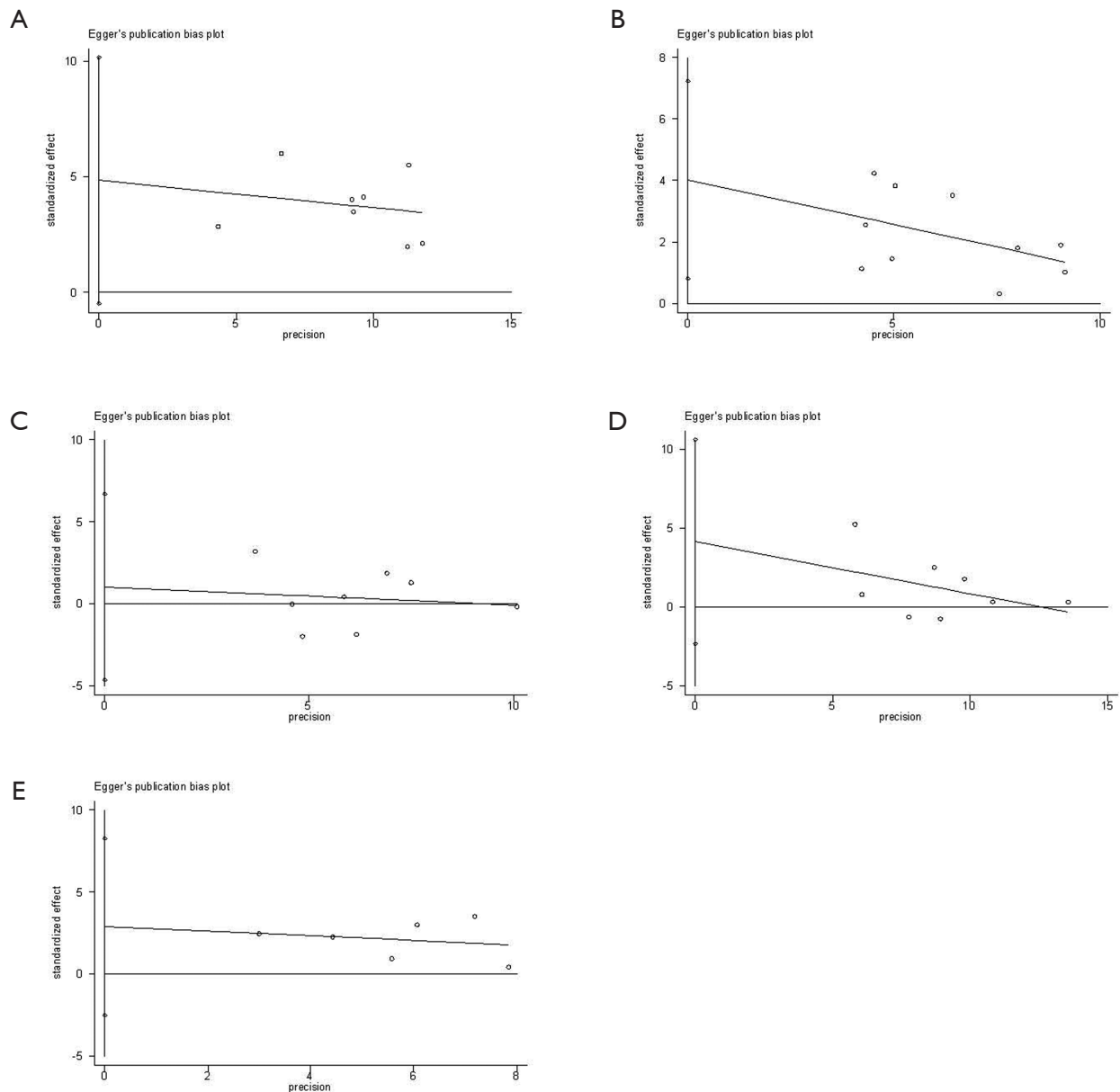


Figure S17 Egger's plots to detect the publication bias of eligible trials on ORR by PD-L1 expression level. (A) PD-L1 non-selective patients, (B) PD-L1 expression $\geq 50\%$, (C) 1-49%, (D) PD-L1-positive and (E) PD-L1-negative. PD-L1, programmed death ligand 1; ORR, objective response rate.

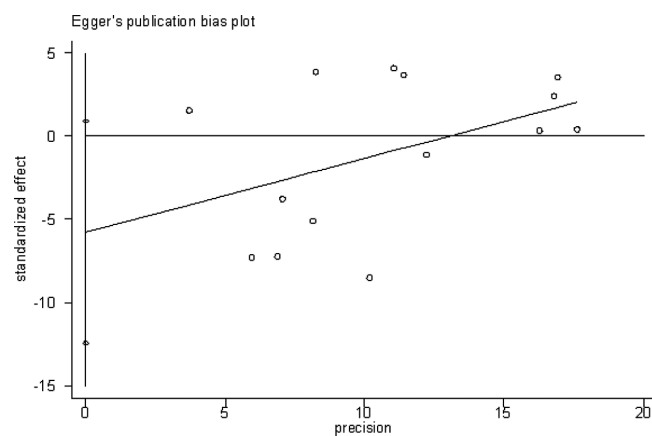


Figure S18 Egger's plots to detect the publication bias of eligible trials on tr-SAE for overall NSCLC patients. NSCLC, non-small cell lung cancer; tr-SAE, treatment-related severe adverse event.