


# The relationship between pneumonitis and programmed cell death-1/programmed cell death ligand 1 inhibitors among cancer patients

## A systematic review and meta-analysis

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### Abstract

**Background:** We put the meta-analysis into practice to reveal the relationship between the incidence risk of immune-related pneumonitis and the use of programmed cell death-1 (PD-1) and ligand 1 (PD-L1) inhibitors related pneumonitis in cancer patients.

**Method:** The meta-analysis was put into practice according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Odds ratio (OR) was evaluated by random effect model.

**Results:** After screening and eligibility assessment, 33 clinical trials involving 19,854 patients were selected and used for the final meta-analysis after selection criteria checked. Compared with chemotherapy, the use of PD-1/PD-L1 inhibitors alone increased the incidence risk of all-grade (OR = 4.29, 95% confidence interval: [2.97, 6.19],  $P < .00001$ ) and grade 3 to 5 immune-related pneumonitis (OR = 3.53, 95% confidence interval: [2.04, 6.11],  $P < .00001$ ). Similar trend could also be found when PD-1/PD-L1 inhibitors were prescribed alone or in combination with other anti-tumor therapies.

**Conclusion:** Whether PD-1/PD-L1 inhibitors were used alone or combined with other antitumor drugs, the incidence risk of immune-related pneumonitis would be increased.

**Abbreviations:** CI = confidence interval, NSCLC = non-small cell lung cancer, OR = odds ratio, PD-1 = programmed cell death-1, PD-L1 = programmed cell death ligand 1, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCC = renal cell carcinoma, RE = random effect.

**Keywords:** cancers, immune-related, meta-analysis, pneumonitis, programmed cell death-1/programmed cell death ligand 1

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DX, HL, MX, and AF contributed equally to this work.

This meta-analysis is just a reorganization and analysis of all the data related to clinical trials. No medical ethics issues were involved.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The authors announced that there was no conflicts of interest needed to be reported in relation to this meta-analysis.

The authors report no conflicts of interest.

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## 1. Introduction

The programmed death 1 (PD-1) receptor, expressed on activated T cells, binds to the ligands PD-L1 and PD-L2, which are expressed by tumor cells and invasive immune cell.<sup>[1]</sup> The expression of PD-L1 is common in non-small cell lung cancer (NSCLC) patients, and the interaction of PD-1 with PD-L1 and PD-L2 ligands suppress T cell activation and promotes tumor immune escape.<sup>[2,3]</sup> Since the phase 1 study of nivolumab monotherapy displayed durable antitumor activity and encouraging survival for metastatic melanoma, colorectal cancer, castrate-resistant prostate cancer, NSCLC, or renal cell carcinoma (RCC),<sup>[4–6]</sup> more and more clinical trials involving PD-1/PD-L1 inhibitors were put into practice for all kinds of cancer patients.<sup>[7–40]</sup> While many clinical trials had achieved encouraging and satisfactory clinical results, a variety of therapeutic side effects had also emerged and drawn our attention to deal with them.<sup>[7–40]</sup> Pneumonitis was one of the PD-1/PD-L1 related treatment side effects, which was reported in several studies.<sup>[7–40]</sup>

Pneumonitis, occurred in PD-1/PD-L1 inhibitor related therapy, was considered to be a kind of interstitial pneumonia and referred as a relatively uncommon but serious and potentially life threatening side effects leading to treatment-related death. It had been considered as one of the events of special interest in clinical work.<sup>[6,14,18,35,41–44]</sup> Though it was a very low incidence of complications, it had an important impact on the prognosis of patients with lung cancer, especially for the discontinuation of PD-1 inhibitor related treatment.<sup>[14,18,35]</sup> With more and more reports of the results of phase III clinical trials, we are able to comprehensively evaluate the incidence risk of immune-related pneumonitis.<sup>[7–40]</sup> In order to reveal the relationship between the incidence risk of pneumonitis and the use of PD-1/PD-L1 drugs in clinical trials involving as many tumor types as possible, we designed this meta-analysis study.

## 2. Methods

### 2.1. Search methods and study selection

We put a systematic search of the literature into practice, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to search materials,<sup>[45]</sup> to select clinical trials involving PD1/PD-L1 inhibitors in cancer patients. Original studies, including information of clinical trials with PD1/PD-L1 related regimens for cancer patients, involving monotherapy or combination therapy, were checked by a PubMed search. The literature searching time range is limited from January 1, 2015 to February 27, 2019 with keywords just as follows: “PD-1/PD1,” “PD-L1/PDL-1,” “nivolumab/BMS-963558,” “pembrolizumab/MK-3475,” “atezolizumab/MPDL3280A,” “PD-1 inhibitor,” “PD-L1 inhibitor,” “cancer,” “random clinical trial,” “RCT,” “CTLA-4,” “pneumonitis.” Selected studies were limited to human beings displayed in full text, abstract, or poster form. The specific searching history of PubMed, according to the participants, interventions, comparisons, outcomes (PICOS) searching strategy recommended by the Cochrane Collaboration,<sup>[45]</sup> was provided in Supplemental Digital Content (Supplemental Material I, <http://links.lww.com/MD/E973>). Four members of our team (Dongmei Xu, Hongmei Liu, Meiyi Xiang, and Alei Feng) were designated for checking their eligibility.

The criteria for enrolled clinical trials:

- (1) available information for PD1/PD-L1 related drugs and controls;

- (2) pneumonitis but pneumonia was collected for evaluating odds ratio (OR) with 95% confidence interval (CI) or other evaluable indicators such as risk ratio, hazard ratio, and so on;
- (3) definite cancer diagnosis by typical imaging changes or pathological biopsy.

Exclusion criteria:

- (1) single arm clinical trial;
- (2) pneumonitis was not shown in any arm and/or cohort;
- (3) studies were presented with incomplete results or data;
- (4) involved combination regimens with other therapies other than PD1/PD-L1 inhibitors.

Any discrepancies in trials selections were resolved through consultation and the corresponding author was responsible for the final decision.

### 2.2. Data extraction and outcome of interest

The collection of the data from all clinical trials was finished referred to the criteria suggested by the Cochrane Collaboration.<sup>[46]</sup> All involving patients prescribed with PD1/PD-L1 inhibitor drugs and the number of patients with pneumonitis of all grades were collected from eligible studies. The trial phase, National Clinical Trial (NCT) number, tumor type, drug type, dose, and prescription regimen were gathered. If only pneumonia but pneumonitis was displayed, we would ask for some help from the corresponding author of the article to determine whether the 2 were deemed to be the same disease. If no data of pneumonitis or pneumonia was found, the study would be excluded from the final analysis. The treatment regimen was divided into subgroups according to the type of experimental group and control group. Sometimes, according to the actual situation, we divide the extracted data into multiple subgroup types. The data collection of PD1/PD-L1 involving drugs was performed independently by 2 members of our team, and then the comparison was made for checking the conformity of the data selection. The corresponding author of the meta-analysis was responsible for all discrepancies and had the right for the final decision. The primary objectives were pneumonitis of all grade and grade 3 to 5. Both all-grade and grade 3 to 5 pneumonitis data would be used for the final comprehensive meta-analysis.

### 2.3. Evaluation of study quality and publication bias

The qualities of all enrolled studies were evaluated by Newcastle–Ottawa scale, Funnel plot, and Egger test, which were proposed by the Cochrane Collaboration.<sup>[45,47,50–52]</sup> Four members of our team (Dongmei Xu, Hongmei Liu, Meiyi Xiang, and Alei Feng) were appointed to evaluate the quality of all enrolled clinical trials. The content of the evaluation, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting, would be gathered and shown in Supplemental Digital Content (Fig. S1, <http://links.lww.com/MD/E968>).<sup>[7–39]</sup> Harbord test was used to check publication bias for all enrolled clinical trials.<sup>[49]</sup>  $P < .05$  was taken as publication bias.

### 2.4. Effect model and assessment of heterogeneity

As the existence of differences among all studies was inevitable, random effect (RE) model was adopted for evaluating all the

data.<sup>[48]</sup> OR of incidence and 95% CI were reported by RE model.  $P < .05$  was considered to be of statistical significance. Heterogeneity was evaluated by Cochrane  $Q$  statistic and the  $I^2$  statistic which was proposed by Higgins and colleagues.<sup>[49]</sup> Heterogeneity was deemed to be low, moderate or high according to the range of  $I^2$  values (<25%, 25%–50%, and >50%). The software of Review Manager 5.3 was used for dealing with all the data. Statistical tests were all 2-sided.

### 3. Results

#### 3.1. Literature search results

Following our preliminary searching principles, 207 PD-1/PD-L1 related clinical trials were collected on the PubMed website, and 63 related literature were collected from other websites or published articles. Thirty-three clinical trials involving 19,854 patients were selected and used for the final comprehensive meta-analysis after selection criteria evaluation.<sup>[7–39]</sup> The PRISMA Flow Diagram chart of the meta-analysis was shown in Figure 1,

and the risk of bias summary was displayed in Supplemental Digital Content (Fig. S1, <http://links.lww.com/MD/E968>). A control group was essential for all clinical trials enrolled in the meta-analysis.<sup>[7–40]</sup> Results from different periods of the same large clinical trial were reported in 2 separate articles.<sup>[21,40]</sup> Only 1 of them was enrolled for the final analysis as the data was consistent with each other.<sup>[21,40]</sup>

According to different prescription regimens, all enrolled trials were divided into 6 groups, which were shown just as follows: Group A (PD-1/PD-L1 vs chemotherapy),<sup>[9,10,15,16–18,22,23,25,26,28,29,31,32,34,37,38]</sup> Group B (PD-1/PD-L1 plus chemotherapy vs chemotherapy),<sup>[11–14,24,35,39]</sup> Group C (PD-1/PD-L1 vs placebo),<sup>[19,20,36]</sup> Group D (PD-1 vs PD-1 + CTLA-4),<sup>[18,21,27]</sup> Group E (PD-1 + CTLA-4 vs CTLA-4),<sup>[21,30]</sup> Group F (PD-1/PD-L1 + targeted therapy vs targeted therapy).<sup>[7,8]</sup>

#### 3.2. Characteristics of identified trials

After screening and eligibility assessment, the basic characteristics of 33 enrolled clinical trials were shown in (Table 1).<sup>[7–40]</sup>

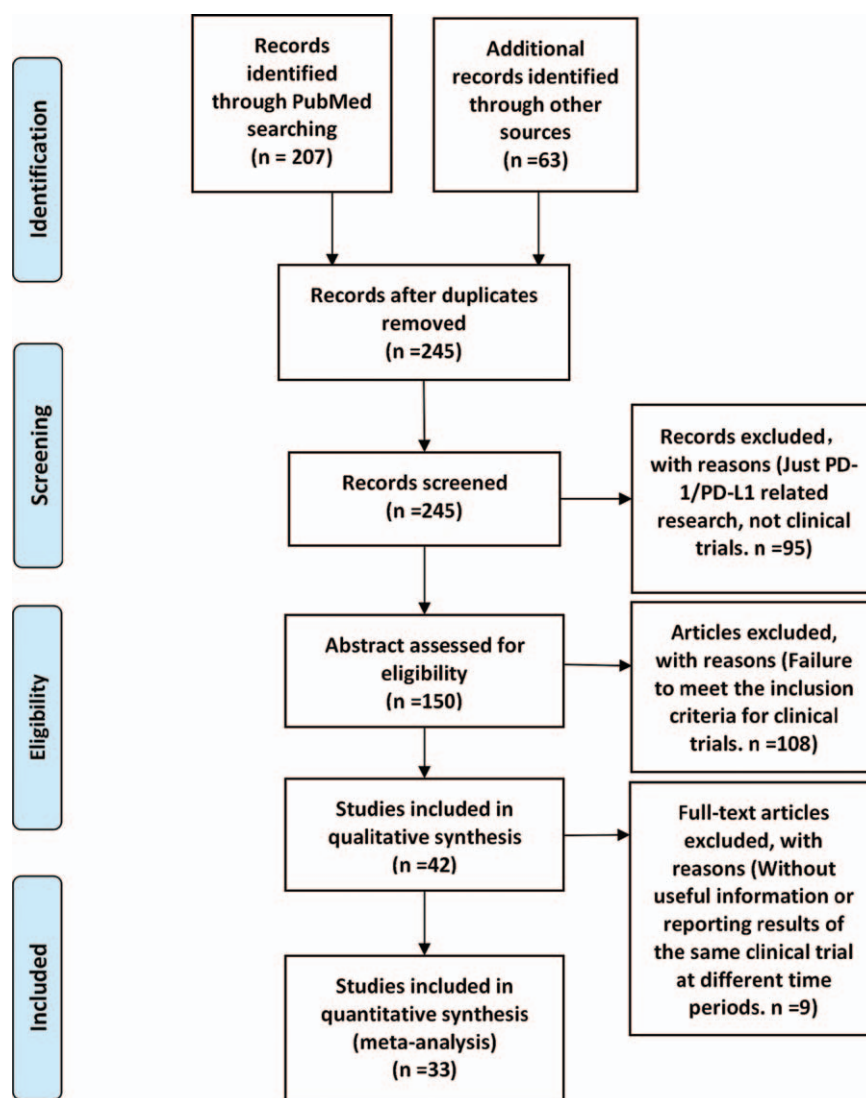


Figure 1. Flow diagram of enrolled clinical trials.

**Table 1**  
**Basic characteristics of 33 enrolled clinical trials.**

No	Reference	Year	NCT number	Drug name	PD-1/ PD-L1	Treatment regimen	Involving patients	Incidence of pneumonitis	Previous therapy	Phase	RCT	Tumor type
1	Ascierto PA, et al <sup>[7]</sup>	2019	NCT02130466	Pembrolizumab	PD-1	Pembrolizumab + dabrafenib + trametinib vs Dabrafenib + trametinib	120	10	NO	II	YES	Melanoma
2	Rini BI, et al <sup>[8]</sup>	2019	NCT02420821	Atezolizumab	PD-L1	Atezolizumab + bevacizumab vs sunitinib	897	12	NO	III	YES	RCC
3	Mok TSK, et al <sup>[9]</sup>	2019	NCT02220894	Pembrolizumab	PD-1	Pembrolizumab vs chemotherapy	1241	56	NO	III	YES	NSCLC
4	Cohen EEW, et al <sup>[10]</sup>	2019	NCT02252042	Pembrolizumab	PD-1	Pembrolizumab vs (methotrexate, docetaxel, cetuximab)	480	13	YES	III	YES	HNSCC
5	Schmid P, et al <sup>[11]</sup>	2018	NCT02425891	Atezolizumab	PD-L1	Atezolizumab + Nab-paclitaxel vs Nab-paclitaxel	890	15	NO	III	YES	Breast Cancer
6	Horn L, et al <sup>[12]</sup>	2018	NCT02763579	Atezolizumab	PD-L1	Atezolizumab + etoposide + carboplatin vs etoposide + carboplatin	394	7	NO	III	YES	SCLC
7	Socinski MA, et al <sup>[13]</sup>	2018	NCT02366143	Atezolizumab	PD-L1	Atezolizumab + bevacizumab + carboplatin + paclitaxel vs bevacizumab + carboplatin + paclitaxel	787	9	NO	III	YES	NSCLC
8	Paz-Ares L, et al <sup>[14]</sup>	2018	NCT02775435	Pembrolizumab	PD-1	Pembrolizumab + carboplatin + paclitaxel vs carboplatin + paclitaxel	558	24	NO	III	YES	NSCLC
9	Barlesi F, et al <sup>[15]</sup>	2018	NCT02395172	Avelumab	PD-L1	Avelumab vs docetaxel	792	15	YES	III	YES	NSCLC
10	Shitara K, et al <sup>[16]</sup>	2018	NCT02370498	Pembrolizumab	PD-1	Pembrolizumab vs paclitaxel	570	8	YES	III	YES	Gastric or Junction Cancer
11	Hida T, et al <sup>[17]</sup>	2018	NCT02008227	Atezolizumab	PD-L1	Atezolizumab vs docetaxel	101	3	YES	III	YES	NSCLC
12	Hellmann MD, et al <sup>[18]</sup>	2018	NCT02477826	Nivolumab	PD-1	Nivolumab plus ipilimumab	1537	34	NO	III	YES	NSCLC
13	Eggermont AMM, et al <sup>[19]</sup>	2018	NCT02362594	Pembrolizumab	PD-1	Pembrolizumab vs placebo	1011	20	NO	III	YES	Melanoma
14	Kang YK, et al <sup>[20]</sup>	2017	NCT02267343	Nivolumab	PD-1	Nivolumab vs placebo	491	1	YES	III	YES	Gastric or Junction Cancer
15	Wolchok JD, et al <sup>[21]</sup>	2017	NCT01844505	Nivolumab	PD-1	Nivolumab vs ipilimumab or nivolumab + ipilimumab	937	32	NO	III	YES	Melanoma
16	Bellmunt J, et al <sup>[22]</sup>	2017	NCT02256436	Pembrolizumab	PD-1	Pembrolizumab vs chemotherapy	521	12	YES	III	YES	UC
17	Rittmeyer A, et al <sup>[23]</sup>	2017	NCT02008227	Atezolizumab	PD-L1	Atezolizumab vs docetaxel	1187	6	YES	III	YES	NSCLC
18	Langer CJ, et al <sup>[24]</sup>	2016	NCT02039674	Pembrolizumab	PD-1	Pembrolizumab + pemetrexed + carboplatin vs Pemetrexed + carboplatin	121	3	NO	II	YES	NSCLC
19	Reck M, et al <sup>[25]</sup>	2016	NCT02142738	Pembrolizumab	PD-1	pembrolizumab vs chemotherapy	304	10	NO	III	YES	NSCLC
20	Ferris RL, et al <sup>[26]</sup>	2016	NCT02105636	Nivolumab	PD-1	Nivolumab vs (methotrexate, docetaxel, or cetuximab)	347	6	YES	III	YES	HNSCC
21	Antonia SJ, et al <sup>[27]</sup>	2016	NCT01928394	Nivolumab	PD-1	Nivolumab + nivolumab + ipilimumab	213	8	YES	III	N/A	SCLC
22	Fehrenbacher L, et al <sup>[28]</sup>	2016	NCT01903993	Atezolizumab	PD-L1	Atezolizumab vs docetaxel	277	4	YES	II	YES	NSCLC
23	Herbst RS, et al <sup>[29]</sup>	2016	NCT01905657	Pembrolizumab	PD-1	Pembrolizumab vs docetaxel	991	37	YES	II/III	YES	NSCLC
24	Hodi FS, et al <sup>[30]</sup>	2016	NCT01927419	Nivolumab	PD-1	Nivolumab + ipilimumab vs ipilimumab	140	9	NO	III	YES	Melanoma
25	Borghaei H, et al <sup>[31]</sup>	2015	NCT01673867	Nivolumab	PD-1	Nivolumab vs docetaxel	555	4	YES	III	YES	NSCLC
26	Brahmer J, et al <sup>[32]</sup>	2015	NCT01642004	Nivolumab	PD-1	Nivolumab vs docetaxel	260	6	YES	III	YES	NSCLC
27	Wolter RJ, et al <sup>[33]</sup>	2015	NCT01668784	Nivolumab	PD-1	Nivolumab vs everolimus	803	74	YES	III	YES	RCC
28	Weber JS, et al <sup>[34]</sup>	2015	NCT01721746	Nivolumab	PD-1	Nivolumab vs chemotherapy	370	5	YES	III	YES	Melanoma
29	Gandhi L, et al <sup>[35]</sup>	2018	NCT02578680	Pembrolizumab	PD-1	Pembrolizumab + chemotherapy vs chemotherapy	439	17	NO	III	YES	NSCLC
30	Antonia SJ, et al <sup>[36]</sup>	2018	NCT02125461	Durvalumab	PD-L1	Durvalumab vs placebo	709	78	YES	III	YES	NSCLC
31	Kato K, et al <sup>[37]</sup>	2019	NCT02569242	Nivolumab	PD-1	Nivolumab vs chemotherapy	417	6	YES	III	YES	OSCC
32	Burness B, et al <sup>[38]</sup>	2019	NCT02358031	Pembrolizumab	PD-1	Pembrolizumab alone or with chemotherapy vs cetuximab + chemotherapy	863	37	NO	III	YES	HNSCC
33	Paz-Ares L, et al <sup>[39]</sup>	2019	NCT03043872	Durvalumab	PD-L1	Durvalumab + Etoposide + Cisplatin vs Etoposide + Cisplatin	531	9	NO	III	YES	SCLC

HNSCC = head-and-neck squamous cell carcinoma, N/A = no available, NSCLC = non-small cell lung cancer, OSCC = oesophageal squamous cell carcinoma, RCC = renal cell carcinoma, RCT = randomized controlled trial, SCLC = small cell lung cancer, UC = urothelial carcinoma.

The involving PD-1 inhibitors were nivolumab (n=11),<sup>[18,20,21,26,27,30–34,37]</sup> and pembrolizumab (n=12),<sup>[7,9,10,14,16,19,22,24,25,29,35,38]</sup> while the involving PD-L1 inhibitors were atezolizumab (n=7),<sup>[8,11–13,17,23,28]</sup> durvalumab (n=2),<sup>[36,39]</sup> and avelumab (n=1).<sup>[15]</sup> Among all enrolled clinical trials, 28 were phase III,<sup>[8–23,25,26,30–39]</sup> 3 was phase II,<sup>[7,24,28]</sup> 1 was phase II/III,<sup>[29]</sup> and 1 was phase I/II.<sup>[27]</sup> The tumor types in 33 clinical trials involved NSCLC (n=15),<sup>[9,13–15,17,18,23–25,28,29,31,32,35,36]</sup> small cell lung cancer (n=3),<sup>[12,27,39]</sup> urothelial cancer (n=1),<sup>[22]</sup> breast cancer (n=1),<sup>[11]</sup> head and neck squamous cell carcinoma (n=3),<sup>[10,26,38]</sup> melanoma (n=5),<sup>[7,19,21,30,34]</sup> RCC (n=2),<sup>[8,33]</sup> oesophageal squamous cell carcinoma (n=1),<sup>[37]</sup> and advanced gastric or gastro-oesophageal junction cancer (n=2).<sup>[16,20]</sup> Thirty-two clinical trials were reported to be randomized controlled trial,<sup>[7–26,28–39]</sup> while the information of 1 clinical trial was unavailable.<sup>[27]</sup> Seventeen clinical trials were reported with previous platinum-based antitumor regimens before PD-1/PD-L1 inhibitors prescription,<sup>[10,15–17,20,22,23,26–29,31–34,36,37]</sup> while PD-1/PD-L1 inhibitors were taken as the first line therapy choice for the other 16 clinical trials.<sup>[7–9,11–14,18,19,21,24,25,30,35,38,39]</sup>

### 3.3. Risk of bias

Newcastle–Ottawa scale was used for the evaluation of study quality and risk of bias.<sup>[47]</sup> Evaluation indexes, including 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), and selective reporting (reporting bias), were checked and summarized in Supplemental Digital Content (Fig. S1, <http://links.lww.com/MD/E968>).<sup>[17–39]</sup> Harbord test was taken for the assessment of publication bias and shown in the form of funnel plots, which were provided in Supplemental Digital Content (Fig. S2, <http://links.lww.com/MD/E969>, Fig. S3, <http://links.lww.com/MD/E970>, and Fig. S5, <http://links.lww.com/MD/E972>).<sup>[17–20,22–32,34–39]</sup>

### 3.4. OR of pneumonitis for the Group A (PD-1/PD-L1 vs chemotherapy)

Seventeen enrolled clinical trials, related to the regimen PD-1/PD-L1 inhibitors versus chemotherapy, were taken to make meta-analysis about the incidence risk of pneumonitis by grade.<sup>[9,10,15,16–18,22,23,25,26,28,29,31,32,34,37,38]</sup> Pneumonitis of all-grade was taken to be evaluated first. In order to improve the accuracy and reliability of the analysis results and clarify the possibility of various biases, different subgrouping approaches were taken into account. The analysis results were presented in the form of forest plots and funnel plots, which were provided in (Fig. 2B and C) and Supplemental Digital Content (Fig. 2E; Figs. S2A, S2B, S2C, and S2E, <http://links.lww.com/MD/E969>).<sup>[9,10,15,16–18,22,23,25,26,28,29,31,32,34,37,38]</sup> Ten lung cancer-related clinical trials, accounted for the largest proportion among 17 enrolled clinical trials, were separately listed for analysis and displayed in (Fig. 2D) and Supplemental Digital Content (Fig. S2D, <http://links.lww.com/MD/E969>).<sup>[9,15,17,18,23,25,28,29,31,32]</sup>

The results of the analysis related to the incidence risk of all grade pneumonitis, shown in different subgrouping approaches, were gathered at the bottom of each figures (Fig. 2A–C and E) (OR=4.29, 95%CI: [2.97, 6.19],  $I^2=0\%$ ,  $Z=7.77$  [ $P<.00001$ ]).<sup>[9,10,15,16–18,22,23,25,26,28,29,31,32,34,37,38]</sup> The results

suggested that the use of PD-1/PD-L1 inhibitor drugs increased the incidence risk of developing immune-related pneumonitis among all kinds of cancers with significant statistical difference (Fig. 2C). Similar results could also be found in the separate analyses of lung cancer-related clinical trials (OR=4.52, 95%CI: [2.61, 7.83],  $I^2=25\%$ ,  $Z=5.38$  [ $P<.00001$ ]; Fig. 2D),<sup>[9,15,17,18,23,25,28,29,31,32]</sup> especially for the subgroup of PD-1 versus chemotherapy (OR=9.54, 95% CI: [3.63, 25.06],  $I^2=26\%$ ,  $Z=4.58$  [ $P<.00001$ ]; Fig. 2D).<sup>[9,18,25]</sup> The existence of heterogeneity were seen in some individual subgroup analysis results ( $I^2=15\%$ , Fig. 2A;  $I^2=25\%$ , Fig. 2C;  $I^2=26\%$ , Fig. 2D). When a full subgroup analysis was performed, no heterogeneity could be found (Fig. 2E). The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S2A–E, <http://links.lww.com/MD/E969>).

Just as the incidence risk trend of immune-related pneumonitis for all grades, similar OR could also be seen in the analysis results of pneumonitis for grade 3 to 5 (OR=3.53, 95% CI: [2.04, 6.11],  $I^2=0\%$ ,  $Z=4.50$  [ $P<.00001$ ]) (Fig. 3A–C and E),<sup>[9,10,15–18,22,23,25,26,28,29,31,32,37,38]</sup> especially for the separate analysis of lung cancer related clinical trials (OR=4.91, 95% CI: [2.43, 9.89],  $I^2=0\%$ ,  $Z=4.44$  [ $P<.00001$ ]) (Fig. 3D).<sup>[9,15,17,18,23,25,28,29,31,32]</sup> The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S3A–E, <http://links.lww.com/MD/E970>).<sup>[9,10,15–18,22,23,25,26,28,29,31,32,37,38]</sup> Moderate heterogeneity was seen in the subgroup analysis of PD-1/PD-L1 versus combined chemotherapy ( $I^2=38\%$ , Fig. 3A),<sup>[9,18,22,25,37]</sup> while obvious heterogeneity was shown in another subgroup of nivolumab versus chemotherapy ( $I^2=55\%$ , Fig. 5A).<sup>[18,37]</sup>

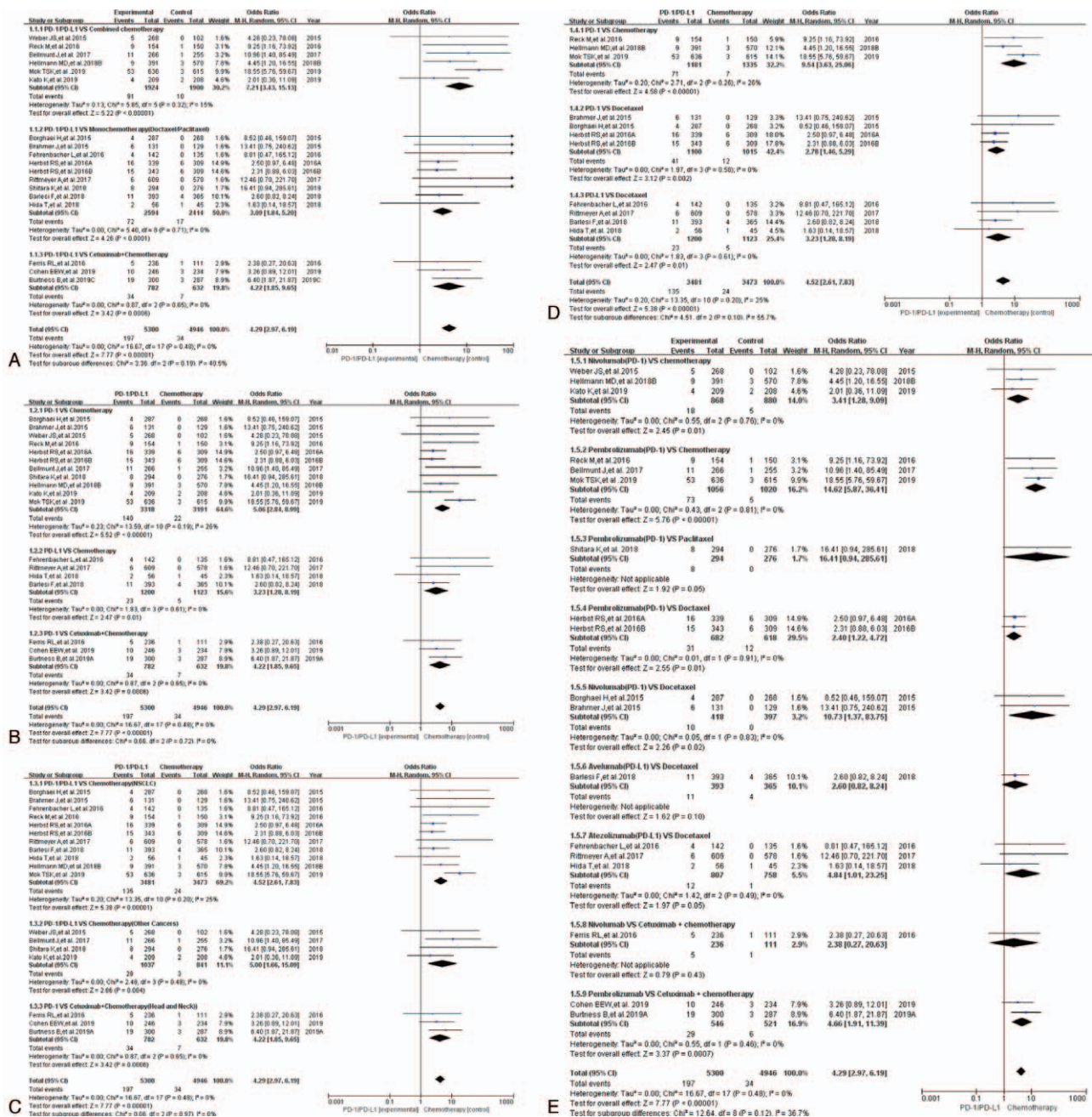
The subgroup analysis results of Group A relating to pneumonitis, including all grade and grade 3 to 5, performed according to the tumor type by RE model, were provided in (Table 2).

### 3.5. OR of pneumonitis for Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy)

Seven enrolled clinical trials were taken into account for further meta-analysis of all grade pneumonitis.<sup>[11–14,24,35,39]</sup> The results of the analysis, shown in different subgrouping approaches, were summarized at the bottom of Figure 4A (OR=3.02, 95% CI: [1.44, 6.37],  $I^2=34\%$ ,  $Z=2.91$  [ $P=.004$ ]).<sup>[11–14,24,35,39]</sup> Moderate heterogeneity was found ( $I^2=34\%$ ). Subgroup analysis results suggested that the source of heterogeneity was the subgroup of PD-L1 plus combined chemotherapy versus chemotherapy ( $I^2=50\%$ , Fig. 4A).<sup>[12,39]</sup> The corresponding funnel plots of OR could be seen in Supplemental Digital Content (Fig. S4A, <http://links.lww.com/MD/E971>). In a word, When PD-1/PD-L1 plus chemotherapy were compared with chemotherapy alone, the incidence of pneumonitis for all grade was significantly higher than that of the control group.

Different from the above results, no significant statistical analysis results were found when all the data were used for calculating the incidence risk of pneumonitis for grade 3 to 5 (OR=1.94, 95% CI: [0.91, 4.12],  $I^2=0\%$ ,  $Z=1.73$  [ $P=.08$ ]).<sup>[11–14,24,35,39]</sup> No obvious heterogeneity was found among all enrolled trials ( $I^2=0\%$ ).<sup>[11–14,24,35,39]</sup> The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S5A, <http://links.lww.com/MD/E972>). No obvious publication bias was found.

The subgroup analysis results of Group B relating to pneumonitis, including all grade and grade 3 to 5, performed



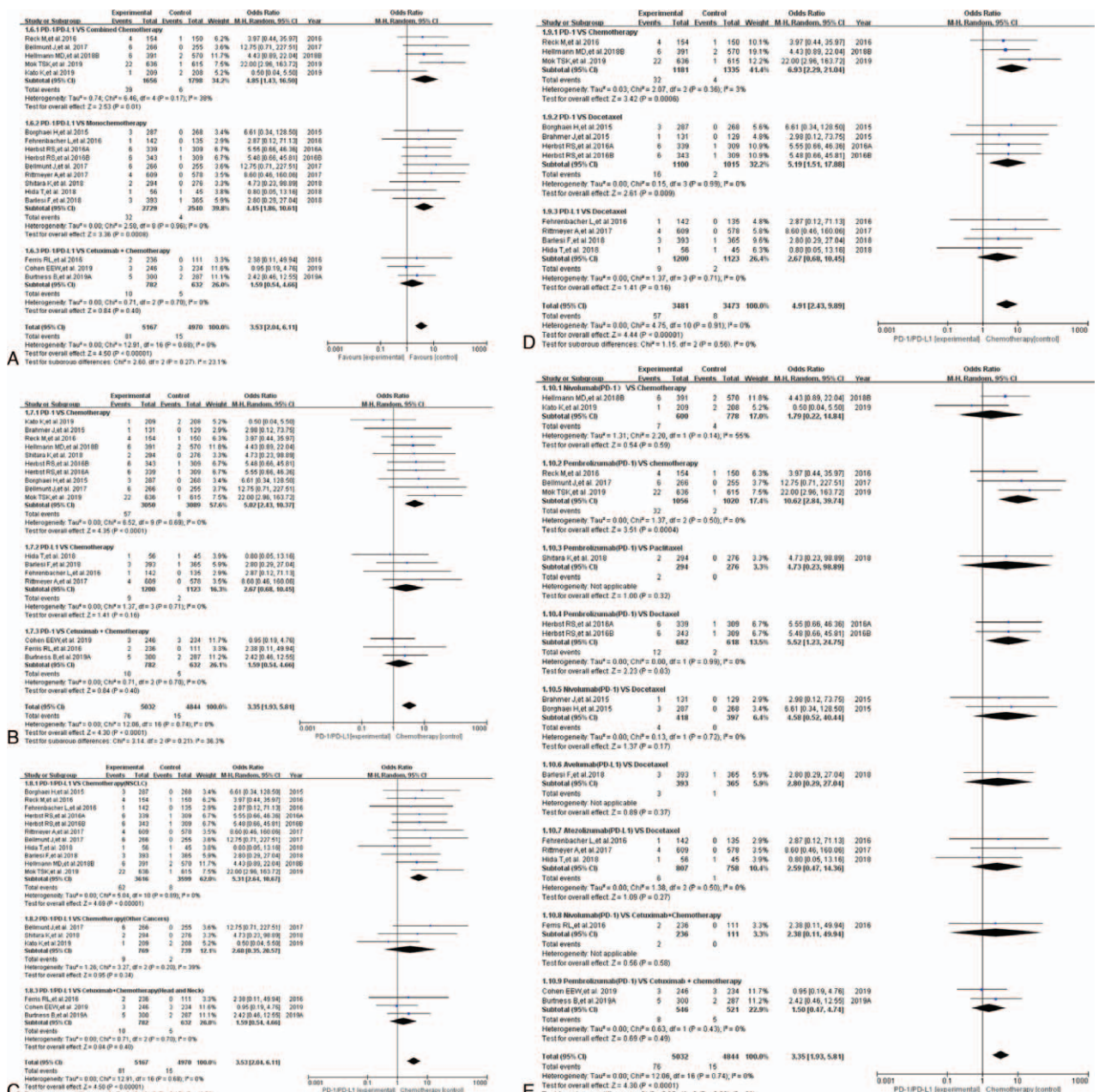
**Figure 2.** Forest plots of all-grade pneumonitis for Group A (PD-1/PD-L1 vs chemotherapy). (A) Incidence risk of all-grade pneumonitis (subgroup analysis based on the composition of the control group's chemotherapy regimen); (B) Incidence risk of all-grade pneumonitis (subgroup analysis based on PD-1, PD-L1, and Cetuximab); (C) Incidence risk of all-grade pneumonitis (subgroup analysis based on tumor types in the control group); (D) Incidence risk of all-grade pneumonitis in NSCLC; (E) Incidence risk of all-grade pneumonitis (subgroup analysis based on specific names of PD-1/PD-L1 inhibitors). NSCLC = non-small cell lung cancer, PD-1 = programmed cell death-1, PD-L1 = programmed cell death ligand 1.

according to the tumor type by RE model, were provided in (Table 2).

**3.6. OR of pneumonitis for Group C (PD-1/PD-L1 vs placebo)**

Compared with placebo, the incidence risk of pneumonitis for all grade was significantly higher than that of the control group, and the OR results were shown in Figure 4B (OR=2.48, 95% CI:

[1.05, 5.86],  $I^2 = 36\%$ ,  $Z = 2.07$  [ $P = .04$ ]).<sup>[19,20,36]</sup> Through subgroup analysis, we could conclude that moderate heterogeneity ( $I^2 = 36\%$ ) might originate from this subgroup (durvalumab vs placebo).<sup>[36]</sup> The corresponding funnel plots were shown in Supplemental Digital Content (Fig. S4B, <http://links.lww.com/MD/E971>). No obvious publication bias was found. No significant statistical analysis results were found when all the data were taken to calculate the incidence risk of pneumonitis for grade 3 to 5 (OR=1.49, 95% CI: [0.53, 4.22],  $I^2 = 0\%$ ,  $Z =$



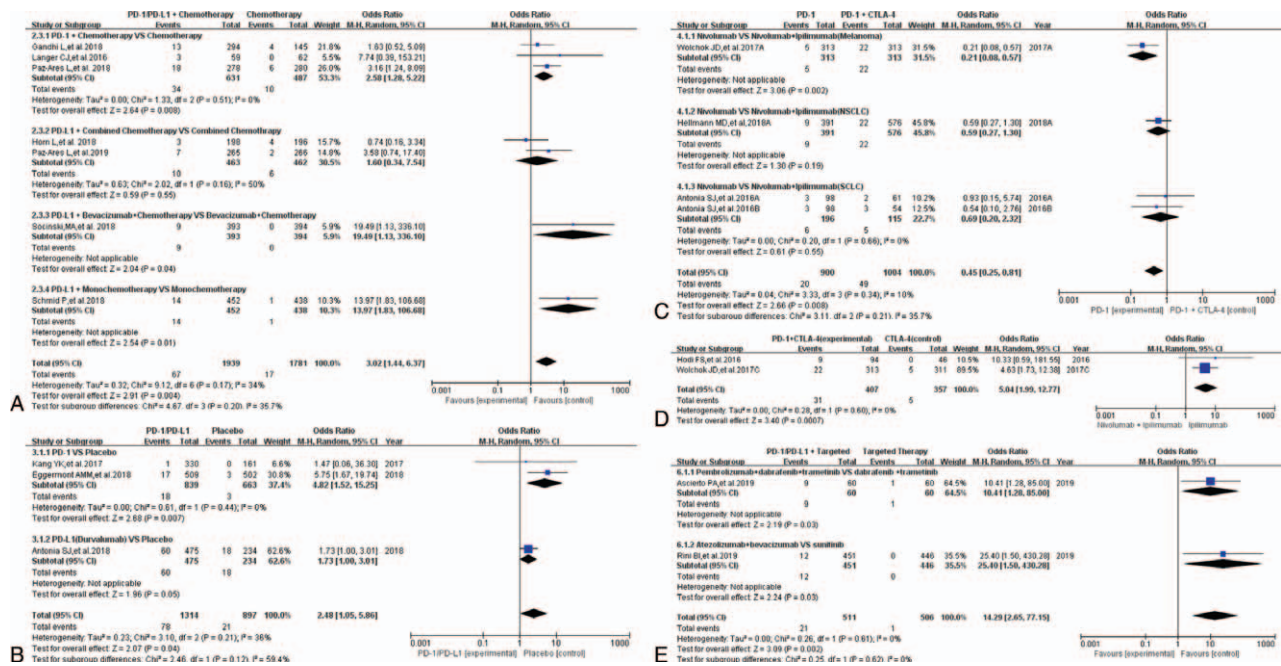
**Figure 3.** Forest plots of grade 3 to 5 pneumonitis for Group A (PD-1/PD-L1 vs chemotherapy). (A) Incidence risk of grade 3 to 5 pneumonitis (subgroup analysis based on the composition of the control group's chemotherapy regimen); (B) Incidence risk of grade 3 to 5 pneumonitis (subgroup analysis based on PD-1, PD-L1, and Cetuximab); (C) Incidence risk of grade 3 to 5 pneumonitis (subgroup analysis based on tumor types in the control group); (D) Incidence risk of grade 3 to 5 pneumonitis in NSCLC; (E) Incidence risk of grade 3 to 5 pneumonitis (subgroup analysis based on specific names of PD-1/PD-L1 inhibitors.). NSCLC = non-small cell lung cancer, PD-1 = programmed cell death-1, PD-L1 = programmed cell death ligand 1.

0.75 [P=.45]; Fig. 5B).<sup>[19,20,36]</sup> No obvious heterogeneity was found among all enrolled trials ( $I^2=0\%$ ).<sup>[19,20,36]</sup> The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S5B, <http://links.lww.com/MD/E972>). No obvious publication bias was found.

**3.7. OR of pneumonitis for Group D (PD-1/PD-L1 vs PD-1/PD-L1 + CTLA-4)**

Three clinical trials, related to melanoma, NSCLC, and small cell lung cancer separately, were put into meta-analysis.<sup>[18,21,27]</sup>

Compared with the control group of PD-1/PD-L1 inhibitors plus CTLA-4, the incidence risk of pneumonitis for all grade was significantly lower (OR=0.45, 95% CI: [0.25, 0.81],  $I^2=0\%$ ,  $Z=2.66$  [P=.008]; Fig. 4C),<sup>[18,21,27]</sup> while no significant statistical difference was seen in the analysis for grade 3 to 5 (OR=0.60, 95% CI: [0.27, 1.36],  $I^2=0\%$ ,  $Z=1.23$  [P=.22]; Fig. 5C).<sup>[18,21,27]</sup> No obvious heterogeneity was found among all enrolled trials ( $I^2=0\%$ ).<sup>[18,21,27]</sup> The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S5C, <http://links.lww.com/MD/E972>). No obvious publication bias was found.

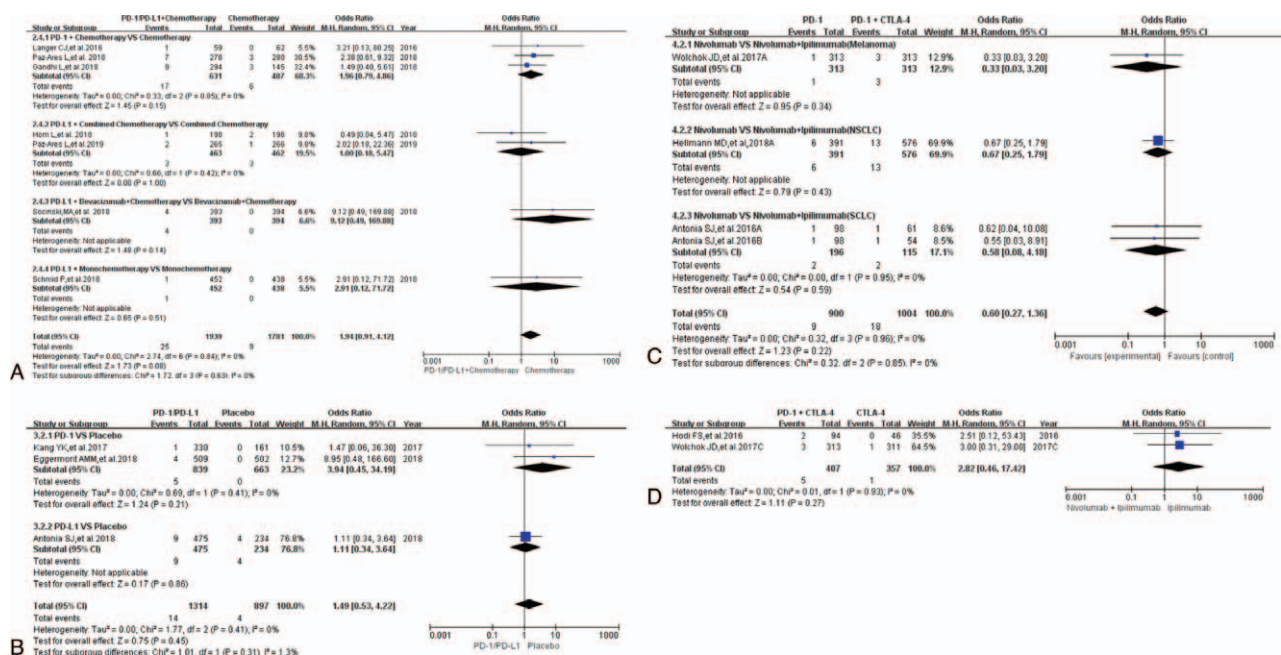


**Figure 4.** Forest plots of all-grade pneumonitis for Group B–F. (A) Incidence risk of all-grade pneumonitis for Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy). (B) Incidence risk of all-grade pneumonitis for Group C (PD-1/PD-L1 vs Placebo). (C) Incidence risk of all-grade pneumonitis for Group D (PD-1 vs PD-1 + CTLA-4). (D) Incidence risk of all-grade pneumonitis for Group E (PD-1 + CTLA-4 vs CTLA-4). (E) Incidence risk of all-grade pneumonitis for Group F (PD-1/PD-L1 + Targeted vs Targeted Therapy).

**3.8. OR of pneumonitis for Group E (PD-1/PD-L1 + CTLA-4 vs CTLA-4)**

Two clinical trials about melanoma were put into meta-analysis.<sup>[21,30]</sup> Compared to the control group of CTLA-4, the

incidence risk of pneumonitis for all grade was significantly higher (OR=5.04, 95% CI: [1.99, 12.77],  $I^2=0\%$ ,  $Z=3.40$  [ $P=.0007$ ]; Fig. 4D),<sup>[21,30]</sup> while no significant statistical difference was seen in the analysis for grade 3 to 5 (OR=2.82,



**Figure 5.** Forest plots of grade 3 to 5 pneumonitis for Group B–D. (A) Incidence risk of grade 3 to 5 pneumonitis for Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy); (B) Incidence risk of grade 3 to 5 pneumonitis for Group C (PD-1/PD-L1 vs Placebo); (C) Incidence risk of grade 3 to 5 pneumonitis for Group D (PD-1 vs PD-1 + CTLA-4); (D) Incidence risk of grade 3 to 5 pneumonitis for Group E (PD-1 + CTLA-4 vs CTLA-4). PD-1 = programmed cell death-1, PD-L1 = programmed cell death ligand 1.



**Table 2**  
The results of meta-analysis performed according to the tumor type.

No	Treatment regimen	Tumor type	OR of pneumonitis	95% CI	Z	P	Grade
1	PD-1 vs chemotherapy	NSCLC	9.54	[3.36, 25.36]	4.58	<.00001	All grade
2	PD-1 vs docetaxel	NSCLC	2.78	[1.46, 5.29]	3.12	.002	All grade
3	PD-L1 vs docetaxel	NSCLC	3.23	[1.28, 8.19]	2.47	.01	All grade
4	PD-1 vs (methotrexate, docetaxel, or cetuximab)	Head-and-neck	4.22	[1.85, 9.65]	3.42	.0006	All grade
5	PD-1/PD-L1 + chemotherapy vs chemotherapy	NSCLC	2.97	[1.39, 6.32]	2.82	.005	All grade
6	PD-L1 + chemotherapy vs chemotherapy	SCLC	1.60	[0.34, 7.54]	0.59	.55	All grade
7	Nivolumab + ipilimumab vs ipilimumab	Melanoma	5.04	[1.99, 12.77]	3.40	.0007	All grade
8	PD-1 vs chemotherapy	NSCLC	6.93	[2.29, 21.04]	3.42	.0006	Grade 3–5
9	PD-1 vs docetaxel	NSCLC	5.19	[1.51, 17.88]	2.61	.009	Grade 3–5
10	PD-L1 vs docetaxel	NSCLC	2.67	[0.68, 10.45]	1.41	.16	Grade 3–5
11	PD-1/PD-L1 + chemotherapy vs chemotherapy	NSCLC	2.24	[0.94, 5.35]	1.82	.07	Grade 3–5
12	PD-L1 + chemotherapy vs chemotherapy	SCLC	1.00	[0.18, 5.47]	0.00	1.00	Grade 3–5

CI=confidence interval, NSCLC=non-small cell lung cancer, OR=odds ratio, SCLC=small cell lung cancer.

95% CI: [0.46, 17.42],  $I^2=0\%$ ,  $Z=1.11$  [ $P=.27$ ]; Fig. 5D).<sup>[21,30]</sup> No obvious heterogeneity was found among all enrolled trials ( $I^2=0\%$ ).<sup>[21,30]</sup> The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S5D, <http://links.lww.com/MD/E972>). No obvious publication bias was found.

**3.9. OR of pneumonitis for Group F (PD-1/PD-L1 + targeted vs targeted therapy)**

Two clinical trials, related to melanoma and RCC separately, were put into meta-analysis.<sup>[7,8]</sup> Compared to the control group of targeted therapy, the incidence risk of pneumonitis for all grade was significantly higher (OR=14.29, 95% CI: [2.65, 77.15],  $I^2=0\%$ ,  $Z=3.09$  [ $P=.002$ ]; Fig. 4E).<sup>[7,8]</sup> No information of pneumonitis for grade 3 to 5 could be found. No obvious heterogeneity was found ( $I^2=0\%$ ).<sup>[7,8]</sup> The corresponding funnel plots were provided in Supplemental Digital Content (Fig. S5E, <http://links.lww.com/MD/E972>). No obvious publication bias was found.

**4. Discussion**

PD-1/PD-L1 related antitumor therapy had been improving outcomes for all kinds of malignant diseases.<sup>[7–40,53,54]</sup> Some of them had been used as the first line choice alone or combined with chemotherapy.<sup>[7–9,11–14,18,19,21,24,25,30,35,38,39]</sup> However, as the range of use expanded, the potential exposure to immune-related adverse events associated with these PD-1/PD-L1 inhibitors also increased. Pneumonitis, an immune-related adverse event, occurred in PD-1/PD-L1 inhibitor related therapy and considered to be a kind of interstitial pneumonia, had been referred as an uncommon and potentially devastating side effects, leading to treatment-related death and had been considered as one of the events of special interest.<sup>[6,14,18,35,41–44]</sup> PD-1/PD-L1 inhibitors had been administered in various ways in clinical trials.<sup>[7–40]</sup> Therefore, in order to comprehensively evaluate the relationship between PD-1/PD-L1 and the incidence risk of immune-related pneumonitis, it is necessary to comprehensively evaluate the different modes of administration after grouping, and then to finish the meta-analysis of each group.<sup>[7–40]</sup>

The process of the meta-analysis was put into practice by us according to the PRISMA guidelines.<sup>[45,47,50–52]</sup> After screening and eligibility evaluation, a total of 33 enrolled clinical trials involving 19,854 cancer patients were collected for the final

consolidation and comprehensive meta-analysis.<sup>[7–39]</sup> The PRISMA flow diagram of the meta-analysis was listed in (Fig. 1). Thirty-three clinical trials, assessed by Newcastle–Ottawa scale,<sup>[47]</sup> were considered to be of better quality showing in Supplemental Digital Content (Fig. S1, <http://links.lww.com/MD/E968>).<sup>[7–39]</sup> Therefore, we could reduce the possibility of bias in the analysis results due to the quality of the clinical trials included in the study.<sup>[47–50,52]</sup> Among all clinical trials enrolled in the study, slight differences are inevitable, so a RE model is considered to be a better choice for more accurate results.<sup>[45–52]</sup> All enrolled trials were divided into 6 groups (Group A–F) according to different prescription regimens, and RE model was used to deal with all the data.<sup>[7–39]</sup> The meta-analysis results of OR, displayed in the form of forest and funnel plots, were shown in (Figs. 2–5) and Supplemental Digital Content (Fig. S2–5, <http://links.lww.com/MD/E969>).<sup>[7–20,22–32,34–39]</sup>

Seventeen clinical trials, involving PD-1/PD-L1 alone versus chemotherapy (Group A), are the most common type among 33 clinical trials.<sup>[9,10,15,16–18,22,23,25,26,28,29,31,32,34,37,38]</sup> Compared with chemotherapy, the results suggested that the use of PD-1/PD-L1 inhibitors increased the incidence risk of immune-related pneumonitis for all grades in cancer patients (OR=4.29, 95% CI: [2.97, 6.19],  $I^2=0\%$ ,  $Z=7.77$  [ $P<.00001$ ]), while such incidence risk trend could also be obtained in the analysis results of grade 3 to 5 immune-related pneumonitis (OR=3.53, 95% CI: [2.04, 6.11],  $I^2=0\%$ ,  $Z=4.50$  [ $P<.00001$ ]; Fig. 3A–C and E).<sup>[9,10,15–18,22,23,25,26,28,29,31,32,37,38]</sup> Through different subgroup analysis for all grade pneumonitis, it was found that moderate heterogeneity (Fig. 2B and C) mainly originated from those clinical trials related to NSCLC (Fig. 2D). So, we separately listed this part of the clinical data for further subgroup analysis. The analysis results displayed that the heterogeneity might mainly originate from 3 clinical trials in the subgroup of PD-1 versus chemotherapy ( $I^2=26\%$ ; Fig. 2D).<sup>[9,18,25]</sup> Most of the enrolled clinical trials were used for the analysis of grade 3 to 5 pneumonitis (Fig. 3A–E).<sup>[9,10,15–18,22,23,25,26,28,29,31,32,37,38]</sup> When those 3 clinical trials were taken for the analysis of grade 3 to 5 pneumonitis,<sup>[9,18,25]</sup> the heterogeneity was low ( $I^2=3\%$ ; Fig. 3D).<sup>[9,18,25]</sup> Therefore, we concluded that the heterogeneity was mainly related to the data changes in those 3 clinical trials.<sup>[9,18,25]</sup> The funnel plots were provided in Supplemental Digital Content (Fig. S2, <http://links.lww.com/MD/E969> and Fig. S3, <http://links.lww.com/MD/E970>). No obvious publication bias was found among them.

Compared with placebo, the incidence risk of immune-related pneumonitis for all grade was significantly higher in the experimental group than that of the control group (OR = 2.48, 95% CI: [1.05, 5.86],  $I^2 = 36\%$ ,  $Z = 2.07$  [ $P = .04$ ]).<sup>[19,20,36]</sup> Through subgroup analysis, we could conclude that moderate heterogeneity ( $I^2 = 36\%$ ) might originate from this subgroup (durvalumab vs placebo).<sup>[36]</sup> When PD-1/PD-L1 inhibitors plus other anti-tumor treatments were compared with the use of one of the antitumor treatments alone, the incidence risks of immune-related pneumonitis were increased (Fig. 4A and C–E). All the above analysis results were considered to be statistical significant. When all the above enrolled clinical trials were taken into account for further analysis of grade 3 to 5, the trend that PD-1/PD-L1 inhibitors increased the risk of developing immune-related pneumonitis could only be found in Group B (PD-1/PD-L1 + chemotherapy vs chemotherapy) (OR = 1.94, 95% CI: [0.91, 4.12],  $I^2 = 0\%$ ,  $Z = 1.73$  [ $P = .08$ ]; Fig. 5A).<sup>[11–14,24,35,39]</sup> No significant statistical analysis results were found (Fig. 5A–D).<sup>[7,8,11–14,18–21,24,30,35,36,39]</sup> Taking all enrolled clinical trials into account, we speculated that they might be related to the lack of clinical trials included in the subgroup analysis and the lower incidence rate of immune-related pneumonitis (Fig. 5A–D).<sup>[7,8,11–14,18–21,24,30,35,36,39]</sup> No heterogeneity was found among them (Fig. 4A, C–E, Fig. 5A–D).<sup>[7,8,11–14,18–21,24,27,30,35,36,39]</sup> Funnel plots were provided in Supplemental Digital Content (Fig. S4A–E, <http://links.lww.com/MD/E971> and Fig. S5A–D, <http://links.lww.com/MD/E972>).<sup>[7,8,11–14,18–21,24,27,30,35,36,39]</sup> No obvious asymmetry of the funnel plots were found, so we concluded that there might be no obvious publication bias Supplemental Digital Content (Fig. S4A–E, <http://links.lww.com/MD/E971> and Fig. S5A–D, <http://links.lww.com/MD/E972>).<sup>[7,8,11–14,18–21,24,27,30,35,36,39]</sup>

Although the clinical trials included in this study had been evaluated for higher quality, there were still some limitations. There were too few trials enrolled in some groups to make a meta-analysis about the relationship between incidence risk of pneumonitis and PD-1 and PD-L1 inhibitors.<sup>[21,33]</sup> In some subgroups, the number of clinical trials included was too few to draw a definite analytical conclusion (Fig. 5A–D).<sup>[7,8,11–14,18–21,24,30,35,36,39]</sup>

Although pneumonitis was relatively rare immune-related adverse events, they might cause devastating or even fatal outcomes if not promptly identified and treated appropriately.<sup>[6,14,18,35,41–44]</sup> For the treatment of immune-related pneumonitis, some treatment options have been reported and recommended in NSCLC.<sup>[55]</sup> More clinical trials and mechanism research for immune-related pneumonitis are still needed.

In a word, Compared with chemotherapy, placebo or other anti-tumor therapies, the results suggested that the use of PD-1/PD-L1 increased incidence risk of immune-related pneumonitis.

## 5. Conclusions

Whether PD-1/PD-L1 inhibitors were used alone or combined with other antitumor drugs, the incidence risk of immune-related pneumonitis would be increased.

## Author contributions

The corresponding author (Yuan Tian) had the right to keep and deal with all the primary data of the meta-analysis, and had the final responsibility for the decision to submit it for publication.

Yuan Tian, Dongmei Xu, Hongmei Liu, Meiyi Xiang, and Mei Tian had the full data of the paper. Donghua Li, and Yantao Mao were responsible for the collection of clinical data. Li Zhang and Shuisheng Zhang were appointed for gathering online data and evaluating the quality of the data.

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