**Molecular
Cancer
Therapeutics**

Risk of Pneumonitis Associated with Programmed Cell Death 1 Inhibitors in Cancer Patients: A Meta-analysis

Sheng Zhang[1], Fei Liang[1], Ji Zhu[1], and Qiang Chen[2]

Abstract

Pneumonitis, a rare but potentially life-threatening adverse event in cancer patients receiving programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitors, has been reported in case reports, clinical trials, and retrospective studies. We performed a systematic review and meta-analysis to calculate the RR of pneumonitis associated with the use of PD-1/L1 inhibitors in randomized clinical trials (RCT). We searched MED-LINE, Embase, the Cochrane Central Register of Controlled Trials, trial registers, conference proceedings, review articles, and reference lists of trial publications for all relevant RCTs comparing PD-1/L1 inhibitors to control with available data on pneumonitis. The pooled incidence, RR, and 95% confidence intervals (CI) were calculated using fixed effects or random effects model according to the heterogeneity of included trials. Twelve RCTs were eligible for the meta-analysis, yielding a total of 5,775 patients included in trials evaluating a PD-1 inhibitor; no eligible trials evaluated a PD-L1 inhibitor. The pooled incidence of all-grade pneumonitis for patients treated with PD-1 inhibitors was 3.2% (95% CI, 2.3–4.5), and that of high-grade pneumonitis was 1.1% (95% CI, 0.7–1.7). The RR of all-grade and high-grade pneumonitis was 4.36 (95% CI, 2.58–7.38) and 2.86 (95% CI, 1.30–6.31), respectively. In a sensitivity analysis, PD-1 inhibitors were also associated with significantly increased risk of pneumonitis per person-month (for all grade, RR = 3.37; 95% CI, 1.97–5.76; for high grade, RR = 2.25; 95% CI, 1.03–4.94). PD-1 inhibitors were associated with a significant increase of all-grade and high-grade pneumonitis both per treatment episode and per person-month. *Mol Cancer Ther; 16(8); 1588–95. ©2017 AACR.*

Introduction

The use of antibodies against programmed cell death 1 (PD-1) or programmed death ligand-1 (PD-L1), which block inhibitory T-cell checkpoints, is a promising new therapy for advanced cancers (1). Recent trials have shown substantial clinical activity of anti-PD-1/L1 antibodies in advanced cancers and led to the approvals of these agents, including nivolumab for melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma, and classical Hodgkin lymphoma; pembrolizumab for melanoma, NSCLC, and head and neck cancers; and atezolizumab for NSCLC and urothelial carcinoma (2–4).

Besides their impressive efficacy, PD-1/L1 inhibitors are also associated with relatively mild toxicity profile (5). However, they are associated with a unique set of toxic effects, which are recognized as immune-related adverse events (IRAE). Among them, pneumonitis is a relatively rare but potentially serious

IRAE, resulting in three treatment-related deaths in a phase I trial (2, 4).

A number of cases with pneumonitis have been reported in patients treated with PD-1/L1 inhibitors in case reports, clinical trials, and retrospective studies (1, 3, 6, 7). The association of PD-1/L1 inhibitors and increased risk of both all-grade and high-grade (grades 3–5) pneumonitis has not been adequately explored in the context of rapidly increasing use of PD-1/L1 inhibitors and available randomized controlled trials (RCT) results. For example, a recent meta-analysis of RCTs investigated risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors and found that immune checkpoint inhibitors were not associated with an increased risk of high-grade pneumonitis based on only three RCTs (8). Another recent meta-analysis analyzed PD-1/L1–associated pneumonitis mainly focusing on early phase I/II and nonrandomized trials (9).

In oncology clinical trials, such as those comparing PD-1/L1 inhibitors with other treatments, patients are generally not treated for a predetermined fixed period of time; rather, they are treated until disease progression, unacceptable toxic events, or withdrawal of consent. Patients are generally followed for safety until a fixed period of time (e.g., 90 or 100 days) after the last dose of study therapy, and further adverse events (AE) are not recorded (3). Because PD-1/L1 inhibitors are beneficial oncology drugs, the patients in these trials often stayed on treatment with active drug much longer than those on the control arm, giving them more time to develop AEs, such as pneumonitis. A wide range of onset time of pneumonitis (ranging from 9 days to 19.2 months) was reported in a recent retrospective study (4). Previous meta-analyses based on incidence per treatment episode (number of

[1]Shanghai Cancer Center and Shanghai Medical College, Fudan University, Shanghai, China. [2]Department of Clinical Biochemistry, School of Public Health Taishan Medical University, Taian, China

S. Zhang and F. Liang contributed equally to this article.

Corresponding Author: Sheng Zhang, Fudan University Shanghai Cancer Center, 270 Dongan Road, Shanghai 200032, China. Phone: 8621-6782-2026; Fax: 8653-3317-7425; E-mail: wozhangsheng@hotmail.com

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patients with AE/safety population), which did not incorporate the difference in safety follow-up time between treatment arms, may overestimate the RR of pneumonitis associated with PD-1/L1 inhibitors (8–10).

The expanding use of a variety of PD-1/L1 inhibitors for the treatment of various types of cancers results in a clear need for a rigorous evaluation of the risk of pneumonitis associated with PD-1/L1 inhibitors. Therefore, we sought to investigate the risk of developing all-grade and high-grade pneumonitis in patients receiving PD-1/L1 inhibitors through a large up-to-date meta-analysis of recent available RCT results.

Materials and Methods

Selection criteria and search strategy

The selection and systematic review of trials was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (11). We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to November 16, 2016. We combined both MeSH and free text words to identify relevant studies. The search strategy is shown in more detail in Supplementary Material. ClinicalTrials.gov was also searched in November 2016 to check for updated data. Conference Proceedings from the American Society of Clinical Oncology and the European Society for Medical Oncology for the years 2011 to 2016 were also hand searched. The latest FDA drug labels of approved agents (nivolumab, pembrolizumab, and atezolizumab) were reviewed to identify additional relevant information. Finally, references in reports of all eligible studies and related reviews were hand searched for other relevant citations.

Eligibility

The goal of the analysis was to establish any association between pneumonitis and exposure to PD-1/L1 inhibitors; therefore, only RCTs comparing a PD-1/L1 inhibitor against a placebo or control arm were included. Articles were first screened on the basis of title and abstract to identify eligible RCTs. Phase I, single-arm phase II, and randomized trials with a PD-1/L1 inhibitor in all arms were excluded. RCTs reported as meeting abstracts without detailed AE data were also excluded.

Remaining studies were further screened in full text to identify whether data on all-grade (grades 1–5) and/or high-grade (grades 3–5) pneumonitis in both treatment and control arms were available. If multiple articles covered the same study population, the study with the most recent or longer follow-up data was used.

Data collection and outcomes

Pneumonitis has been defined as a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma in Common Terminology Criteria for Adverse Events v4.0 (CTCAE 4.0). Number and grade of treatment-related pneumonitis in both treatment and control arms (if not available, pneumonitis data reported regardless of attribution to study treatment were used) were extracted from text or appendix of the trial publications.

For all eligible trials, we also extracted the following data: first author's name, year of publication, phase of the trial, cancer type, name of PD-1/L1 inhibitor, treatment regimen in both arms, the number of participants evaluable for safety, and safety follow-up time. If safety follow-up time was not reported, it was estimated by median treatment duration plus trial protocol-specified fixed time after the last dose of treatment.

Statistical analysis

We conducted separate analyses for all-grade and high-grade pneumonitis.

We first calculated the incidence and corresponding 95% confidence intervals (CI) of pneumonitis for each treatment arm in each RCT by using number of patients experiencing pneumonitis and total number of patients evaluable for safety (incidence per treatment episode). For the calculation of RR, the primary outcome measure of this study, the incidence of pneumonitis for patients assigned to PD-1 inhibitor were compared with that of patients assigned to control arm in the same trial. For studies reporting zero events in a treatment or control arm, we applied a classic half-integer continuity correction to calculate RR and variance. Statistical heterogeneity between RCTs was assessed by Cochrane's Q statistic, and inconsistency was quantified with the I^2 statistic [100% × (Q−df)/Q]. Pooled incidence, RRs, and risk difference (RD) were calculated using random- or fixed effects models depending on the heterogeneity of included studies. When substantial heterogeneity was not observed (i.e., Cochran Q statistical analysis yielding a P value of ≥ 0.10), the pooled estimate calculated on the basis of the fixed effects model was reported using Mantel–Haenszel method; otherwise, random model was used.

To better understand the relationship between PD-1 inhibitors and pneumonitis, we performed four subgroup analyses: cancer type; treatment mode (combination therapy or monotherapy); control type (PD-1 inhibitors vs. ipilimumab or PD-1 inhibitors vs. chemotherapy); and therapeutic agents (nivolumab or pembrolizumab).

We calculated the total number of person-months of safety follow-up in both PD-1 inhibitor and control arms, and related incidence of all-grade and high-grade pneumonitis per person-month.

We also conducted three extra sensitivity analyses by alternative effect measure (RR vs. OR) and statistical models regarding heterogeneity (random vs. fixed effects) and Mantel–Haenszel exact method without zero-cell correction to further assess the robustness of the results to the choice of this model for the meta-analysis.

The Cochrane Collaboration's tool was used to assess the risk of bias of RCTs included in our study (12). Publication bias was evaluated by using funnel plots (plots of study results against precision) and with the Begg and Egger tests. A two-tailed P value of less than 0.05 without adjustment for multiplicity was considered statistically significant. All statistical analyses were performed using Review Manger 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014) and meta package of R software (version 3.32)

Two authors (S. Zhang and F. Liang) independently screened trials for eligibility, assessed risk of bias, and extracted data from each included trial using standardized forms. Any discrepancy was identified and resolved successfully by the consensus of all authors in this study. We used the κ coefficient to determine the degree of agreement between reviewers. Agreement between reviewers was high (κ = 0.91).

Ethical approval

Because this study is a literature study, ethical approval is not required.

Results

Search results and study characteristics

Our initial search yielded 1,789 reports. After removing obvious duplicates and screening titles and abstracts, we retrieved 15 reports for full-text screening. One report was excluded because of no available pneumonitis data in control arm. Data from one report were not used because updated report of longer follow-up with more complete AEs was available. Another study comparing nivolumab versus everolimus was removed from meta-analysis because everolimus is well known for a high risk of drug-related pneumonitis. No eligible trials evaluating PD-L1 inhibitor were identified. Finally, 12 RCTs were included in the meta-analysis (Fig. 1; refs. 13–24).

The 12 RCTs comprised a total of 5,775 patients. Pneumonitis was graded using CTCAE 4.0 in all trials. Eight trials reported treatment-related pneumonitis, whereas four trials only reported pneumonitis regardless of attribution to study treatment by the investigator. The characteristics of each trial are summarized in Table 1. Cancer types studied included melanoma ($n = 6$), NSCLC ($n = 5$), and head and neck cancer ($n = 1$). Because one trial of melanoma included two treatment arms with different regimens containing PD-1 inhibitor (nivolumab monotherapy

and nivolumab combined with ipilimumab), PD-1 inhibitor monotherapy was evaluated in 10 trials and in 3 trials as combination therapy. The control arms consisted of ipilimumab in 3 trials and chemotherapy in 9 trials. Safety follow-up time was reported or estimable in 11 trials, and patients in PD-1 inhibitor arms were followed for a longer time in 8 trials (Table 1).

Incidence of pneumonitis

A total 111 cases of all-grade pneumonitis were reported among 3,655 patients receiving PD-1 inhibitors in 12 RCTs. The incidence of pneumonitis ranged from 1.1% to 10.6%, with the highest incidence observed in a melanoma trial (15) in which patients received the combination therapy of nivolumab and ipilimumab, and the lowest incidence was observed in a melanoma trial of pembrolizumab monotherapy (19). Using a random effects model for this analysis (heterogeneity test: Q = 0.97, $P < 0.001$, $I^2 = 41.0\%$), the pooled incidence of all-grade pneumonitis was 3.2% (95% CI, 2.3–4.5). Only two trials (23, 24) reported information regarding previous thoracic radiotherapy, and the proportions of patients receiving thoracic radiotherapy were the same between PD-1 inhibitor and control arms. No thoracic radiotherapy information was provided for the patients who developed pneumonitis.
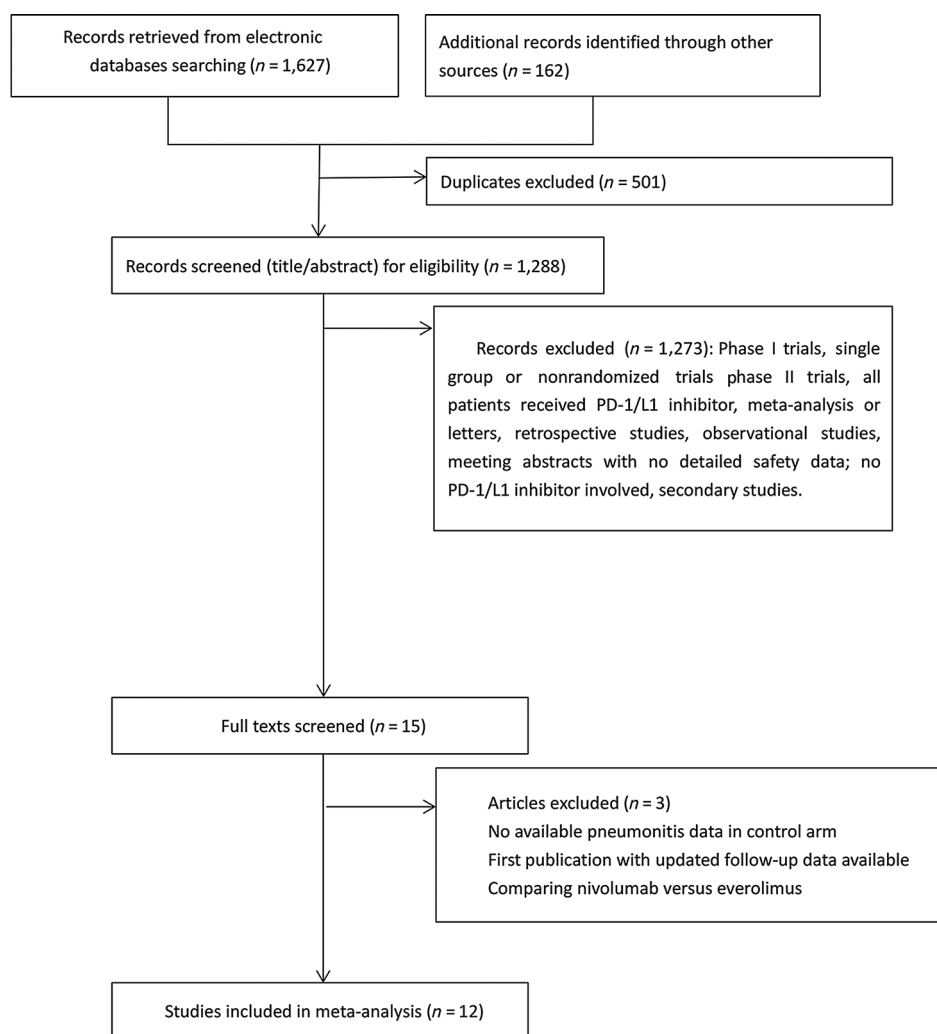

Figure 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart displaying the search and selection process performed.

Table 1. Characteristics of randomized controlled trials included in the meta-analysis

Reference	Phase	Cancer type	PD-1 inhibitor arm						Control arm					
			Drug	Safety follow-up (months)	Number of patients	All-grade pneumonitis	Grade ≥ 3 pneumonitis	Pneumonitis-related death	Drug	Safety follow-up (month)	Number of patients	All-grade pneumonitis	Grade ≥ 3 pneumonitis	Pneumonitis-related death
Borghaei et al, 2015	III	NSCLC	Nivolumab	6.3	287	8	3	0	Docetaxel	6.3	268	1	1	0
Brahmer et al, 2015	III	NSCLC	Nivolumab	7.3	131	6	1	0	Docetaxel	5.6	129	0	0	0
Ferris et al, 2016	III	Head and neck	Nivolumab	5.2	236	5	2	1	Methotrexate, docetaxel, or cetuximab	5.2	111	1	0	0
Herbst et al, 2016	III	NSCLC	Pembrolizumab	6.5	682	26	12	3	Docetaxel	5.0	309	3	1	0
Hodi et al, 2016	III	Melanoma	Nivolumab and ipilimumab	6.3	94	10	3	1	Ipilimumab	6.3	46	0	0	0
Langer et al, 2016[a]	II	NSCLC	Pembrolizumab, carboplatin, and pemetrexed	11	59	3	1	0	Carboplatin and pemetrexed	7.9	62	0	0	0
Larkin et al, 2015	III	Melanoma	Nivolumab	10.8	313	4	1	0	Ipilimumab	6.3	311	5	1	0
			Nivolumab and ipilimumab	6.3	313	20	3	0						
Reck et al, 2016[a]	III	NSCLC	Pembrolizumab	10	154	9	4	0	Platinum-based chemotherapy	6.8	150	1	1	0
Ribas et al, 2015[a]	II	Melanoma	Pembrolizumab	7.3	357	6	2	0	Chemotherapy	5	171	0	0	0
Robert et al, 2015	III	Melanoma	Nivolumab	NR	206	3	0	0	Dacarbazine	NR	205	0	0	0
Robert et al, 2015[a]	III	Melanoma	Pembrolizumab	8.3[b]	555	6	1	0	Ipilimumab	4.7[b]	256	1	1	0
Weber et al, 2015	III	Melanoma	Nivolumab	8.6	268	5	0	0	Chemotherapy	5.3	102	0	0	0

Abbreviation: NR, not reported.
[a]Pneumonitis reported regardless of attribution to study treatment by the investigator.
[b]Mean safety follow-up time.

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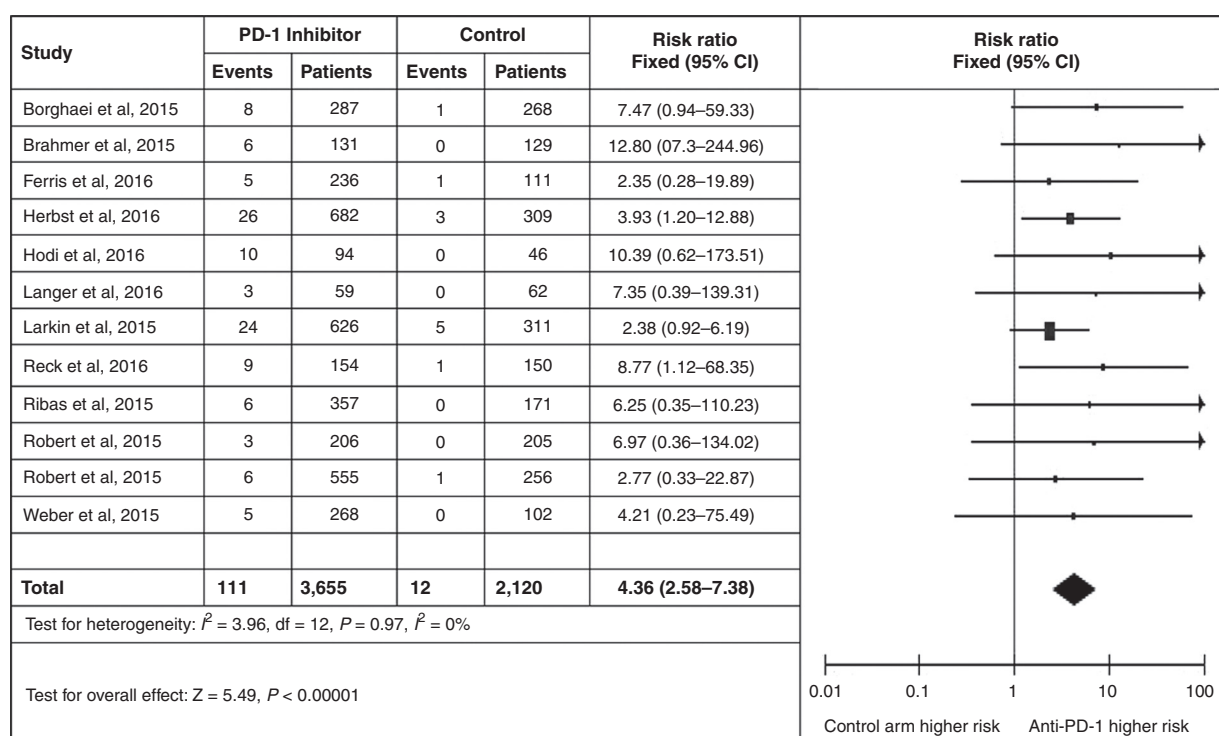
Figure 2.
Forest plot of the risk ratio of all-grade pneumonitis associated with PD-1 inhibitor versus control. CI, confidence interval.

All 12 included RCTs reported the number of high-grade (grade ≥ 3) pneumonitis in the PD-1 inhibitors arms. A total number of 33 patients experienced high-grade pneumonitis, including 5 pneumonitis-related deaths. The incidence of high-grade pneumonitis ranged from 0% to 3.2%. Using a random-effect model (heterogeneity test: Q = 0.95; P = 0.095; I^2 = 26.3%), the pooled incidence of high-grade pneumonitis was 1.1% (95% CI, 0.7–1.7).
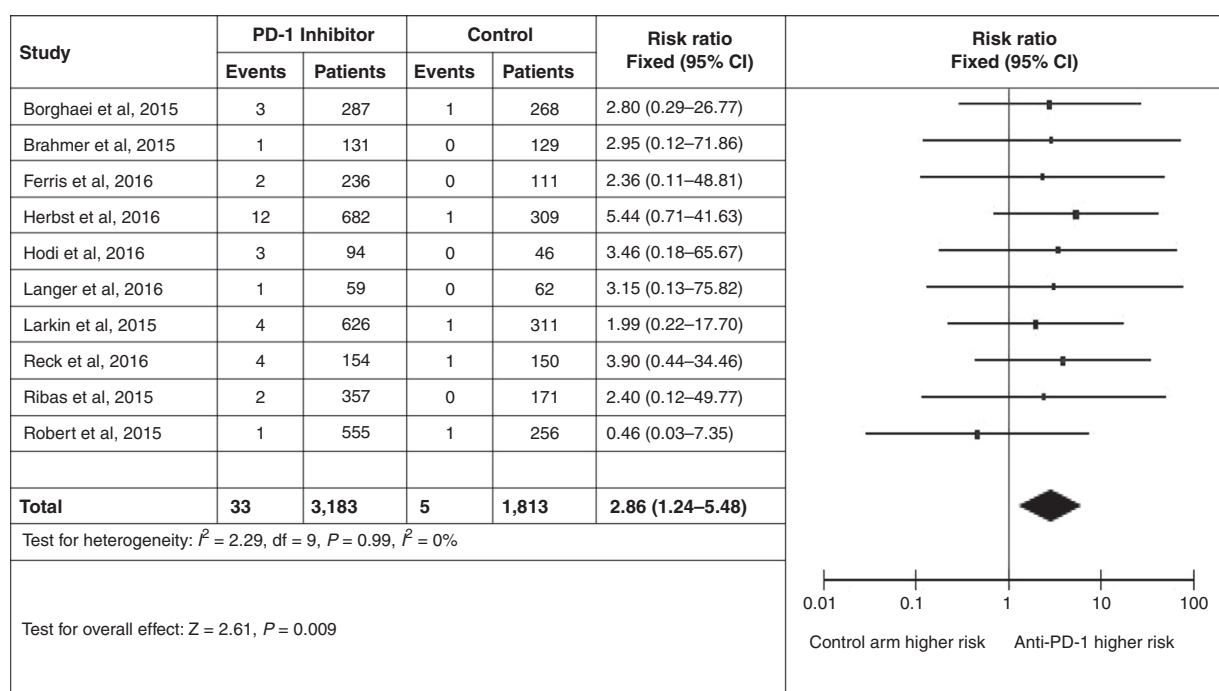
RR of pneumonitis

Among the 5,775 patients in the 12 included RCTs, the pooled RR of all grade pneumonitis was 4.36 (95% CI, 2.58–7.38; P < 0.001) based on fixed-effect model (heterogeneity test: Q = 3.96, P = 0.97, I^2 = 0%) using Mantel–Haenszel method (Fig. 2).

Pooled RD of all-grade pneumonitis was 2.26% (95% CI, 1.31–3.21; P < 0.001). Among different cancer types, the highest RR was observed in NSCLC (RR = 5.98; 95% CI, 2.62–13.63), followed by melanoma (RR = 3.52; 95% CI, 1.69–7.34), but no significant difference was found for RR of all-grade pneumonitis among different cancer types. Higher RR was observed in patients receiving combination therapy (RR = 4.94; 95% CI, 2.05–11.90), but the difference was not statistically significant compared with monotherapy (RR = 3.74; 95% CI, 2.11–6.63). There were no statistically significant differences in RRs of different control types (PD-1 inhibitors vs. ipilimumab or PD-1 inhibitors vs. chemotherapy) and therapeutic agents (nivolumab or pembrolizumab; Table 2).

Table 2. Subgroup analysis of RR of all-grade pneumonitis associated with PD-1 inhibitor

		PD-1 inhibitor		Control				P	
Group	Number of trials	Number of events	Number of patients	Number of events	Number of patients	I^2 (%)	RR (95% CI)	RR	Interaction
Cancer type									0.55
NSCLC	5	52	1,313	5	918	0	5.98 (2.62–13.63)	<0.001	
Melanoma	6	54	2,106	6	1,091	0	3.52 (1.69–7.34)	<0.001	
Head and neck cancer	1	5	236	1	111	NA	2.35 (0.28–19.89)	0.43	
Treatment mode									0.60
Combination therapy	3	33	466	5	419	0	4.94 (2.05–11.90)	<0.001	
Monotherapy	10	78	3,189	12	2,012	0	3.74 (2.11–6.63)	<0.001	
Control type									0.29
Versus ipilimumab	3	40	1,275	6	613	0	3.06 (1.35–6.95)	0.008	
Versus chemotherapy	9	71	2,380	6	1,507	0	5.45 (2.72–10.91)	<0.001	
Therapeutic agents									0.70
Nivolumab	7	61	1,848	7	1,172	0	4.08 (2.07–8.05)	<0.001	
Pembrolizumab	5	50	1,807	5	948	0	4.78 (2.08–10.97)	<0.001	

Abbreviations: CI, confidence interval; NA, not applicable.

Study	PD-1 Inhibitor		Control		Risk ratio Fixed (95% CI)	Risk ratio Fixed (95% CI)
	Events	Patients	Events	Patients		
Borghaei et al, 2015	3	287	1	268	2.80 (0.29–26.77)	
Brahmer et al, 2015	1	131	0	129	2.95 (0.12–71.86)	
Ferris et al, 2016	2	236	0	111	2.36 (0.11–48.81)	
Herbst et al, 2016	12	682	1	309	5.44 (0.71–41.63)	
Hodi et al, 2016	3	94	0	46	3.46 (0.18–65.67)	
Langer et al, 2016	1	59	0	62	3.15 (0.13–75.82)	
Larkin et al, 2015	4	626	1	311	1.99 (0.22–17.70)	
Reck et al, 2016	4	154	1	150	3.90 (0.44–34.46)	
Ribas et al, 2015	2	357	0	171	2.40 (0.12–49.77)	
Robert et al, 2015	1	555	1	256	0.46 (0.03–7.35)	
Total	33	3,183	5	1,813	2.86 (1.24–5.48)	

Test for heterogeneity: $I^2 = 2.29$, df = 9, $P = 0.99$, $I^2 = 0\%$

Test for overall effect: Z = 2.61, $P = 0.009$

0.01   0.1   1   10   100

Control arm higher risk   Anti-PD-1 higher risk

Figure 3.
Forest plot of the risk ratio of grade ≥ 3 pneumonitis associated with PD-1 inhibitor versus control. CI, confidence interval.

Two RCTs with zero high-grade pneumonitis in both arms were excluded in the meta-analysis for high-grade pneumonitis. The pooled RR of high-grade pneumonitis of the 10 remaining RCTs was 2.86 (95% CI, 1.30–6.31; $P = 0.009$) based on fixed-effect model (heterogeneity test: Q = 2.61, $P = 0.99$, $I^2 = 0\%$) using Mantel–Haenszel method (Fig. 3). Pooled RD of high-grade pneumonitis was 0.69% (95% CI, 0.26–1.13; $P < 0.001$). Subgroup analysis did not show any significant difference (Supplementary Table S1).

Sensitivity analysis

To determine whether an increased risk of pneumonitis per person-month associated with PD-1 inhibitors compared with control existed, we did a sensitivity analysis by incorporating the difference in safety follow-up time between patients in the PD-1 inhibitors arms and control arms. Pooled RRs of all grade pneumonitis and high-grade pneumonitis per person-month were 3.37 (95% CI, 1.97–5.76; $P < 0.001$) and 2.25 (95% CI, 1.03–4.94; $P = 0.04$) (Supplementary Figs. S1 and S2), respectively.

Additional sensitivity analysis using alternative effect measure (RR vs. OR), statistical models regarding heterogeneity (random vs. fixed effects), and Mantel–Haenszel exact method without zero-cell correction did not find important changes in the pooled RR for both all-grade and high-grade pneumonitis. In a *post hoc* sensitivity analysis by excluding RCTs only reporting pneumonitis regardless of attribution to study treatment by the investigator, the pooled RR was 4.04 (95% CI, 2.24–7.29) for all-grade pneumonitis and 3.29 (95% CI, 1.20–9.07) for high-grade pneumonitis.

Bias assessment

Randomization procedures and allocation concealment were properly reported in all trials. Three trials were double-blinded

and thus judged to be of low risk of performance and detection bias. All studies lacked reporting bias, attrition bias, and other sources of bias not specifically addressed by the Cochrane Collaboration risk of bias tool (Supplementary Table S2).

Publication bias

There was no evidence of publication bias of RR for high-grade pneumonitis (Begg test $P = 0.53$, Egger test $P = 0.37$), but publication bias may exist for all-grade pneumonitis (Begg test $P = 0.41$, Egger test $P = 0.008$). Funnel plots for both all-grade and high-grade pneumonitis were provided in the Supplementary Figs. S3 and S4. Because Egger test may lead to false-positive results with insufficient number of included studies and few events per study (12), we conducted an exploratory sensitivity to adjust by excluding two smaller studies with largest intervention effect (15, 23), and no funnel plot asymmetry was detected ($P = 0.478$, Egger test). Pooled RR of all grade pneumonitis from remaining 10 RCTs was 3.63 (95% CI, 2.15–6.4), showing the robustness of the results.

Discussion

The recent rapidly increasing number of RCTs with PD-1/L1 inhibitors has drawn much attention to the associated treatment-related pneumonitis, which can occur occasionally and may become severe in clinical practice (2, 3). Although a small number of patients with pneumonitis have been reported in RCTs of PD-1/L1 inhibitors, none of these trials were designed to have enough power to assess this rare AE. To our knowledge, this is the first meta-analysis that firmly demonstrated PD-1 inhibitors were significantly associated with increased risk of both all grade and high-grade pneumonitis according to per treatment episode and per person-month.

Previously, some meta-analyses of targeted drug-associated AEs have been challenged due to longer on-treatment and safety follow-up duration than the control group. Those results have been changed to nonsignificant when the calculation was adjusted per person-month (10, 25–27). To overcome this possible confounding, our analysis with sensitivity analysis according to unit of time still confirmed our conclusion. Other strengths of our study include the comprehensive search, careful selection of studies from published and nonpublished trials through various data sources.

The pooled incidence for all-grade and high-grade pneumonitis in patients who received PD-1 inhibitor was 3.2% and 1.1%, respectively, which were lower than that reported by Naidoo and colleagues (5.0% and 1.3%; ref. 4). Several reasons can explain this difference. First, clinical trials are usually not designed specifically to address toxic events; thus, asymptomatic AEs may be ignored in the prospective assessment. One third of patients were asymptomatic at the onset of pneumonitis (4). Our study focused on treatment-related pneumonitis reported in RCTs, while all pneumonitis retrospectively identified were included in the retrospective study (4).

In the subgroup analysis, numerically higher RRs of both all-grade and high-grade pneumonitis were found in trials of NSCLC, combination therapy, chemotherapy control, or nivolumab, but none of these differences were statistically significant. Given the sample size of this meta-analysis, these subgroup analyses may not have enough power to detect or rule out the differences. It needs to be investigated in further studies.

Two previous meta-analyses have assessed the risk of treatment-related pneumonitis among cancer patients receiving PD-1/L1 inhibitors. The first study was a meta-analysis of RCTs investigating risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors. Clinical trials investigating ipilimumab, a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)–blocking antibody, were also included, making the results difficult to interpret (8). They also found that immune checkpoint inhibitors were not associated with an increased risk of high-grade pneumonitis based on only three RCTs. Another meta-analysis compared the incidence of PD-1 inhibitor–related pneumonitis among different tumor types and therapeutic regimens. Phase I and single-arm phase II trials were also included, and RR was not calculated (9). Furthermore, several important large RCTs were published subsequent to the previous reviews, and neither of these studies evaluated the effect of different safety follow-up time and calculated the risk of pneumonitis per person-month. These factors may substantially confound the results and interpretation of meta-analyses. Therefore, our results should better provide the risk of pneumonia associated with PD-1/L1 inhibitors in current literature of RCTs.

Our study has limitations. First, data were abstracted from published clinical trial results; therefore, individual patient information was not available. Second, in this study, publication bias may present in all grade pneumonitis data, which may reflect underreporting of small, negative, or nonsignificant RCTs in the published literature. But given the comprehensive literature research of this study and more than 4-fold RR observed, it is unlikely that underreporting of all-grade pneumonitis data, if exists, will significantly change the results of our study.

It is also noteworthy the stringent eligibility criteria of RCTs may exclude patients with comorbidities (28). For example, generally patients with certain autoimmune diseases and preexisting lung diseases were excluded in RCTs with PD-1/L1 inhibitors (4). As these drugs become used in a more heterogeneous patient population, the incidence of PD-1/L1–associated pneumonitis may be higher than the results synthesized from RCT results. Practicing oncologists need to be aware of this risk and provide continuous monitoring for patients.

In conclusion, this study has demonstrated that PD-1 inhibitors were associated with significant increase in all-grade and high-grade pneumonitis both per treatment episode and per person-month. Given the increasing use of PD-1 inhibitors in cancer patients, it is important for physicians and patients to recognize this risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Zhang, F. Liang, J. Zhu
Development of methodology: S. Zhang, F. Liang, Q. Chen
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Zhang, F. Liang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Zhang, F. Liang
Writing, review, and/or revision of the manuscript: S. Zhang, F. Liang, Q. Chen
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): F. Liang
Study supervision: S. Zhang, F. Liang

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