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ORIGINAL RESEARCH

Pneumonitis and pneumonitis-related death in cancer patients treated with programmed cell death-1 inhibitors: a systematic review and meta-analysis

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Peng-Fei Cui[1–3,*]
Jun-Xun Ma[1,*]
Fei-Xue Wang[1,*]
Jing Zhang[1]
Hai-Tao Tao[1]
Yi Hu[1]

[1]First Department of Medical Oncology, [2]Department of Graduate Administration, Chinese PLA General Hospital, Beijing, [3]Health Bureau of the 75709 Army, Central Theater of the Chinese PLA, Wuhan, China

*These authors contributed equally to this work

Purpose: We conducted a meta-analysis of published clinical trials to determine the relationship between the risks of pneumonitis and pneumonitis-related death and programmed cell death-1 (PD-1) inhibitor treatment in patients with cancer.

Materials and methods: We examined clinical trials from the Medline and Google Scholar databases. Data from original studies and review articles were also cross-referenced and evaluated. Randomized Phase II and Phase III trials of pembrolizumab and nivolumab treatment in patients with cancer were eligible for the analysis. Information about the participants, all-grade and high-grade pneumonitis, and pneumonitis-related death was extracted from each study and analyzed.

Results: After the exclusion of ineligible studies, 12 clinical trials were included in the analysis. The odds ratio (OR) for all-grade pneumonitis after PD-1 inhibitor treatment was 4.59 (95% confidence interval [CI]: 2.51–8.37; $P<0.00001$), and the OR for high-grade pneumonitis after PD-1 inhibitor treatment was 3.83 (95% CI: 1.54–9.48; $P=0.004$). The OR for pneumonitis-related death after PD-1 inhibitor treatment was 2.47 (95% CI: 0.41–14.81; $P=0.32$). Moreover, the OR for all-grade pneumonitis after nivolumab/ipilimumab combination therapy versus nivolumab monotherapy was 3.54 (95% CI: 1.52–8.23; $P=0.003$), and that for high-grade pneumonitis after nivolumab/ipilimumab combination therapy versus nivolumab monotherapy was 2.35 (95% CI: 0.45–12.13; $P=0.31$). Treated cancer appeared to have no effect on the risk of pneumonitis.

Conclusion: Our data showed that PD-1 inhibitors were associated with increased risks of all-grade and high-grade pneumonitis compared with chemotherapy or placebo controls in patients with cancer. However, we noted no significant difference between patients treated with a PD-1 inhibitor and patients treated with control regimens with respect to the risk of pneumonitis-related death.

Keywords: nivolumab, pembrolizumab, PD-1 inhibitors, immune mediated pneumonitis

Introduction

Immune checkpoint inhibitors are unequivocally one of the most important breakthroughs in cancer therapy in the past 10 years.[1] They function by releasing the brakes of the immune system that limit the activation of T-cells, thus boosting the self-immune response against cancer cells.[2] Several checkpoint inhibitors have already been approved and have been in use for years. Ipilimumab (an anti-CTLA-4 monoclonal antibody) was the first inhibitor to be approved for melanoma management in adjuvant

Correspondence: Yi Hu
First Department of Medical Oncology, Chinese PLA General Hospital, 28 Fuxing Road, Haidian, Beijing 100853, China
Tel +86 139 1103 1186
Fax +86 10 6693 9272
Email huyi0401@aliyun.com

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and metastatic settings.[3,4] Nivolumab and pembrolizumab are two programmed cell death-1 (PD-1)-targeted monoclonal antibodies that have been approved for the management of advanced melanoma and for use in previously treated non-small-cell lung cancer (NSCLC).[5–7] Atezolizumab is a novel anti-programmed cell death ligand-1 (PD-L1) monoclonal antibody that has been shown to have remarkable effects on advanced urothelial carcinoma and previously treated NSCLC.[8]

However, immune system activation is detrimental not only to the survival of cancer cells but also to certain types of healthy tissues.[9] Thus, a new group of adverse events, called immune-related adverse events (IRAEs), has been recognized. IRAEs include characteristic cutaneous, gastrointestinal, hepatic, pulmonary, endocrine, and renal events.[10–14] Among them, pneumonitis has been reported to be a relatively uncommon but serious and potentially life-threatening IRAE and has resulted in pneumonitis-related death in several Phase I trials.[7,15,16] Previous studies have demonstrated that the incidence of PD-1 inhibitor-related pneumonitis was increased in NSCLC and renal cell carcinoma and that the incidence of pneumonitis was higher with the use of PD-1 inhibitors than with the use of PD-L1 inhibitors.[17,18] However, there has been no systematic review or meta-analysis assessing the associations between the incidences of pneumonitis and pneumonitis-related death and PD-1 inhibitors. Thus, we conducted a meta-analysis of randomized clinical trials to determine the overall risks of pneumonitis development and pneumonitis-related death in patients with cancer who were treated with different PD-1 inhibitors.

Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement while conducting this systematic review and meta-analysis.[19]

Data sources

A literature review of studies published between January 2000 and March 2017 was conducted using major citation databases, including Medline and Google Scholar, and the search terms "pembrolizumab" OR "nivolumab" OR "PD-1 inhibitors". The search was limited to randomized clinical trials that were published in English and involved human patients with solid tumors.

Study selection

The following studies were included in the analysis: 1) randomized Phase II and III studies involving patients with solid tumors, 2) studies involving participants allocated to groups receiving treatment with a PD-1 inhibitor, and 3) studies for which data regarding the prevalence and incidence of both all-grade (grades 1–4) and high-grade (grades 3–4) pneumonitis or pneumonitis-related death were available. The following articles were excluded from the analysis: 1) reports of Phase I trials and 2) meeting abstracts whose corresponding full-text articles were not published. Independent reviewers screened reports including the above key terms in their titles and abstracts to determine their potential relevance, after which the full texts of relevant articles were retrieved to assess their eligibility for inclusion in the study. The references cited in the relevant articles were also reviewed.

Data extraction and clinical end points

The authors conducted the data extraction independently. Any disagreements regarding the data extracted by the authors were resolved by the achievement of consensus. The following information was extracted from each trial: the first author's name, the date of publication, the trial phase, the underlying diagnosis, the type of immune checkpoint inhibitor, the treatment arms, the total number of patients, the number of pneumonitis events (all-grade and high-grade), and the number of pneumonitis-related deaths. We assessed the quality of each included study using the Jadad scoring system (Table 1).[20] Each parameter in the Jadad scoring system was evaluated and scored, and the total of all the individual parameter scores was defined as the overall score for each study.

The Common Terminology Criteria for Adverse Events, version 4.0, was utilized to uniformly assess toxicity parameters in all the trials included in the analysis.

Statistical analysis

We performed all data analyses using Review Manager 5.3 software (Nordic Cochrane Center, Copenhagen, Denmark).

Table 1 Jadad quality assessment of the included studies

Study	Randomization	Blinding	An account of all patients	Overall score
Ferris et al[22]	2	0	1	3
Weber et al[23]	2	0	1	3
Robert et al[6]	2	2	1	5
Brahmer et al[24]	2	0	1	3
Borghaei et al[25]	2	0	1	3
Motzer et al[26]	2	0	1	3
Herbst et al[27]	2	0	1	3
Reck et al[28]	2	0	1	3
Ribas et al[29]	2	0	1	3
Bellmunt et al[30]	2	0	1	3
Antonia et al[31]	2	0	1	3
Larkin et al[32]	2	2	1	5

Between-study heterogeneity with respect to the outcomes of the studies included in the analysis was evaluated through Cochrane's Q statistic. A result of $P>0.1$ and $I^2<50\%$ indicated that no significant between-study heterogeneity was present. In cases in which no significant heterogeneity was present, we used the fixed-effects model to perform the analysis.[21] Odds ratios (ORs) for pneumonitis (all-grade and high-grade) and pneumonitis-related death and corresponding 95% confidence intervals (CIs) were our principal measures of the risks of these outcomes after immune checkpoint inhibitor treatment. The numbers and types of adverse events affecting the participants who were randomized to receive immune checkpoint inhibitor treatment were compared with those affecting the participants who were randomized to receive the control treatment in each trial. A two-sided $P<0.05$ was considered statistically significant. Publication bias was assessed using funnel plots.

Results

Search results

The searches of PubMed/Medline and other databases yielded 191 potentially relevant citations of clinical trials of PD-1 inhibitors. The schema depicting the process through which studies were included in and excluded from the analysis is shown in Figure 1.

As mentioned above, a total of 12 clinical trials, including 10 Phase III trials and two Phase II trials (Tables 2 and 3), was considered eligible for the meta-analysis. Six trials evaluated nivolumab[23–26] (one of which evaluated nivolumab vs everolimus),[26] four trials evaluated pembrolizumab,[27–30] and two trials compared nivolumab/ipilimumab combination therapy with nivolumab monotherapy.[31,32] Four studies pertained to NSCLC (one of which evaluated advanced squamous NSCLC), four studies evaluated malignant melanoma, one study evaluated squamous cell carcinoma of the

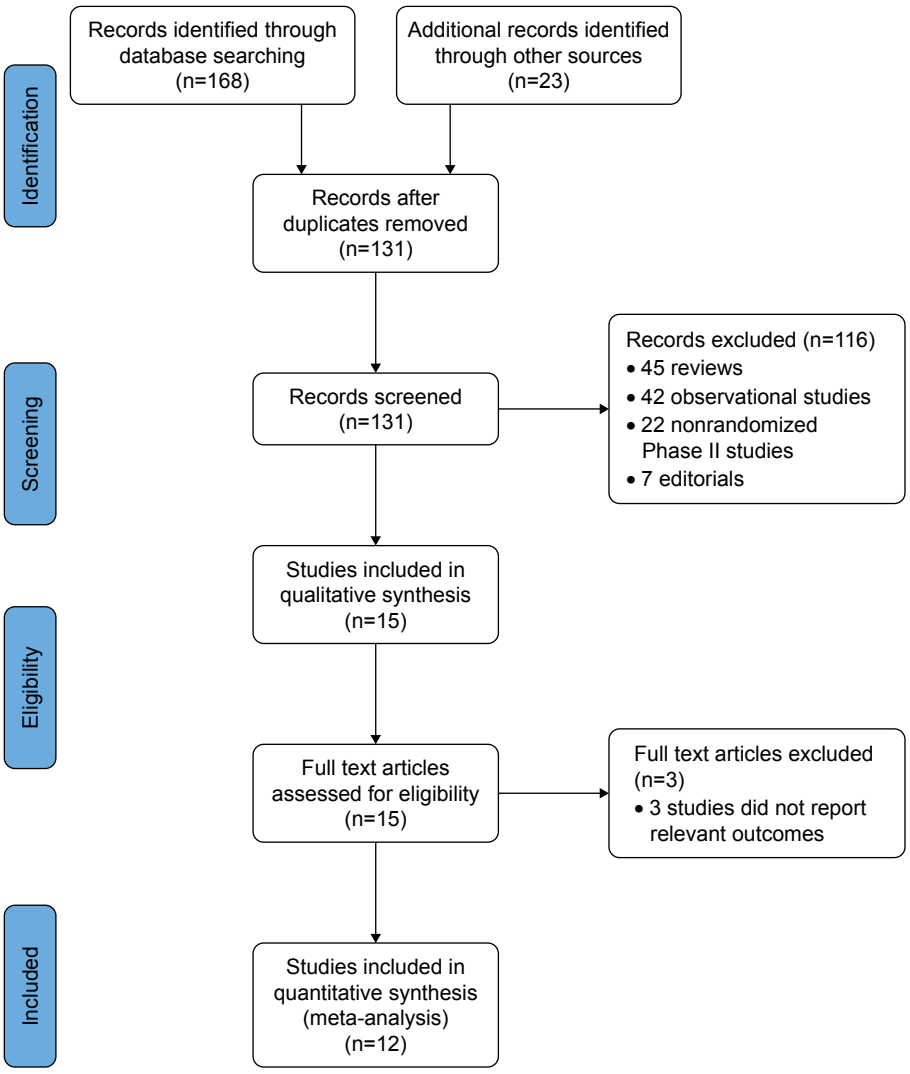

Figure 1 Flowchart of study selection.

Table 2 Baseline characteristics of included studies comparing PD-1 inhibitors to non-PD-1 inhibitors

Study	Study type	Treatment arms	Number of patients	Dose of the PD-1 inhibitor	Indication	All-grade (grades 1–4) pneumonitis	High-grade (grades 3–4) pneumonitis	Pneumonitis-related death
Nivolumab studies								
Ferris et al[22]	Phase III	Arm A: nivolumab Arm B: chemotherapy	Arm A: 236 Arm B: 111	Arm A: nivolumab 3 mg/kg Q2W	Squamous cell carcinoma of the head and neck	Arm A: 5 (2.1%) Arm B: 1 (0.9%)	Arm A: 2 (0.8%) Arm B: 0 (0)	Arm A: 1 (0.4%) Arm B: 0 (0)
Weber et al[23]	Phase III	Arm A: nivolumab Arm B: chemotherapy	Arm A: 268 Arm B: 102	Arm A: nivolumab 3 mg/kg Q2W	Melanoma	Arm A: 5 (1.9%) Arm B: 0 (0)	Arm A: 0 (0) Arm B: 0 (0)	Arm A: 0 (0) Arm B: 0 (0)
Robert et al[6]	Phase III	Arm A: nivolumab Arm B: dacarbazine	Arm A: 206 Arm B: 205	Arm A: nivolumab 3 mg/kg Q2W	Melanoma	Arm A: 3 (1.5%) Arm B: 0 (0)	Arm A: 0 (0) Arm B: 0 (0)	Arm A: 0 (0) Arm B: 0 (0)
Brahmer et al[24]	Phase III	Arm A: nivolumab Arm B: docetaxel	Arm A: 131 Arm B: 129	Arm A: nivolumab 3 mg/kg Q2W	Advanced squamous cell non-small-cell lung cancer	Arm A: 6 (5%) Arm B: 0 (0)	Arm A: 0 (0) Arm B: 0 (0)	Arm A: 0 (0) Arm B: 0 (0)
Borghaei et al[25]	Phase III	Arm A: nivolumab Arm B: docetaxel	Arm A: 287 Arm B: 268	Arm A: nivolumab 3 mg/kg Q2W	Non-squamous non-small-cell lung cancer	Arm A: 8 (3%) Arm B: 1 (<1%)	Arm A: 3 (1%) Arm B: 1 (<1%)	Arm A: 0 (0) Arm B: 0 (0)
Motzer et al[26]	Phase III	Arm A: nivolumab Arm B: everolimus	Arm A: 406 Arm B: 397	Arm A: nivolumab 3 mg/kg Q2W	Advanced renal cell carcinoma	Arm A: 16 (4%) Arm B: 58 (15%)	Arm A: 6 (1%) Arm B: 11 (3%)	Arm A: 0 (0) Arm B: 0 (0)
Pembrolizumab								
Herbst et al[27]	Phase III	Arm A: pembrolizumab Arm B: pembrolizumab Arm C: docetaxel	Arm A: 339 Arm B: 343 Arm C: 309	Arm A: pembrolizumab 2 mg/kg Q3W Arm B: pembrolizumab 10 mg/kg Q3W	Advanced non-small-cell lung cancer	Arm A: 16 (5%) Arm B: 15 (4%) Arm C: 6 (2%)	Arm A: 7 (2%) Arm B: 7 (2%) Arm C: 2 (1%)	Arm A: 2 (0.6%) Arm B: 1 (0.3%) Arm C: 0 (0)
Reck et al[28]	Phase III	Arm A: pembrolizumab Arm B: chemotherapy	Arm A: 154 Arm B: 150	Arm A: pembrolizumab 200 mg Q3W	Non-small-cell lung cancer	Arm A: 9 (5.8%) Arm B: 1 (0.7%)	Arm A: 4 (2.6%) Arm B: 1 (0.7%)	Arm A: 0 (0) Arm B: 0 (0)
Ribas et al[29]	Phase II	Arm A: pembrolizumab Arm B: pembrolizumab Arm C: chemotherapy	Arm A: 178 Arm B: 179 Arm C: 171	Arm A: pembrolizumab 2 mg/kg Q3W Arm B: pembrolizumab 10 mg/kg Q3W	Melanoma	Arm A: 3 (2%) Arm B: 3 (2%) Arm C: 0 (0)	Arm A: 0 (0) Arm B: 2 (1%) Arm C: 0 (0)	Arm A: 0 (0) Arm B: 0 (0) Arm C: 0 (0)
Bellmunt et al[30]	Phase III	Arm A: pembrolizumab Arm B: chemotherapy	Arm A: 266 Arm B: 255	Arm A: pembrolizumab 200 mg Q3W	Advanced urothelial carcinoma	Arm A: 11 (4.1%) Arm B: 1 (0.4%)	Arm A: 6 (2.3%) Arm B: 0 (0)	Arm A: 1 (0.4%) Arm B: 0 (0)

Abbreviations: PD-1, programmed cell death-1; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

Table 3 Direct comparison of different PD-1 inhibitors

Study	Study type	Treatment arms	Number of patients	Dose of the PD-1 inhibitor	Indication	All-grade (grades 1–4) pneumonitis	High-grade (grades 3–4) pneumonitis	Pneumonitis-related death
Antonia et al[31]	Phase II	Arm A: nivolumab Arm B: nivolumab plus ipilimumab Arm C: nivolumab plus ipilimumab	Arm A: 98 Arm B: 61 Arm C: 54	Arm A: nivolumab 3 mg/kg Q2W Arm B: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W Arm C: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W	Recurrent small-cell lung cancer	Arm A: 3 (3%) Arm B: 2 (4%) Arm C: 3 (6%)	Arm A: 1 (1%) Arm B: 1 (2%) Arm C: 1 (2%)	Arm A: 0 (0) Arm B: 0 (0) Arm C: 0 (0)
Larkin et al[32]	Phase III	Arm A: nivolumab Arm B: nivolumab plus ipilimumab Arm C: ipilimumab	Arm A: 313 Arm B: 313 Arm C: 311	Arm A: nivolumab 3 mg/kg Q2W Arm B: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W Ipi 3 mg/kg Arm C: ipilimumab 3 mg/kg Q3W	Melanoma	Arm A: 4 (1.3%) Arm B: 20 (6.4%) Arm C: 5 (1.6%)	Arm A: 1 (0.3%) Arm B: 3 (1%) Arm C: 1 (0.3%)	Arm A: 0 (0) Arm B: 0 (0) Arm C: 0 (0)

Abbreviations: PD-1, programmed cell death-1; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

head and neck, one study evaluated advanced renal cell carcinoma, one study evaluated advanced urothelial carcinoma, and one study evaluated small-cell lung cancer. The interventions evaluated in the analysis included nivolumab monotherapy, pembrolizumab monotherapy, nivolumab/ipilimumab combination therapy, chemotherapy control treatments, placebo control treatments, and everolimus control treatments.

Population characteristics

The data for a total of 6,240 patients were available for analysis. Most of the trials did not include patients with impaired renal, hepatic, or bone marrow function, in accordance with their inclusion and exclusion criteria, and most of the patients enrolled in the indicated studies had an Eastern Cooperative Oncology Group performance status ranging from 0 to 2. The baseline characteristics of the patients included in each trial and data regarding the number of patients in each trial who suffered from pneumonitis (all-grade and high-grade) or experienced pneumonitis-related death are presented in Tables 1 and 2.

Quality of the included studies

The scoring system and the other elements of the Jadad scale, which was used to assess the quality of each of the included studies, are shown in Table 1. Data regarding the parameters used to assess study quality, as well as data pertaining to the randomization and blinding methods used by each study and all the patients enrolled in the analysis, are available. All the studies included in this meta-analysis were of high quality.

Overall incidences of pneumonitis and pneumonitis-related death

For the analysis of overall incidence of pneumonitis and pneumonitis-related death, we considered only study arms receiving PD-1 inhibitors. The incidence of all-grade pneumonitis (grades 1–4) was reported in all the studies and ranged from 1.3% to 5.8%. The incidence of high-grade (grades 3–4) pneumonitis ranged from 0% to 2.6%. The incidence of pneumonitis-related death was also reported in all the included studies and ranged from 0% to 0.6% (two deaths) (Tables 2 and 3).[27]

ORs for all-grade and high-grade pneumonitis and pneumonitis-related death

To evaluate the ORs for all-grade and high-grade pneumonitis, we considered only studies comparing PD-1 inhibitors with a non-PD-1 inhibitor control. Moreover, we excluded the study by Motzer et al[26] from the final analysis because everolimus (the control drug) is known to be associated with a high risk of drug-related pneumonitis. The OR for all-grade pneumonitis was 4.59 (95% CI: 2.51–8.37; $P<0.00001$), and the OR for high-grade pneumonitis was 3.83 (95% CI: 1.54–9.48; $P=0.004$) (Figure 2A and B). The results were classified further according to the type of agent used (nivolumab vs pembrolizumab).

Nivolumab

The OR for all-grade pneumonitis with nivolumab treatment was 5.93 (95% CI: 1.96–17.93; $P=0.002$), and that for

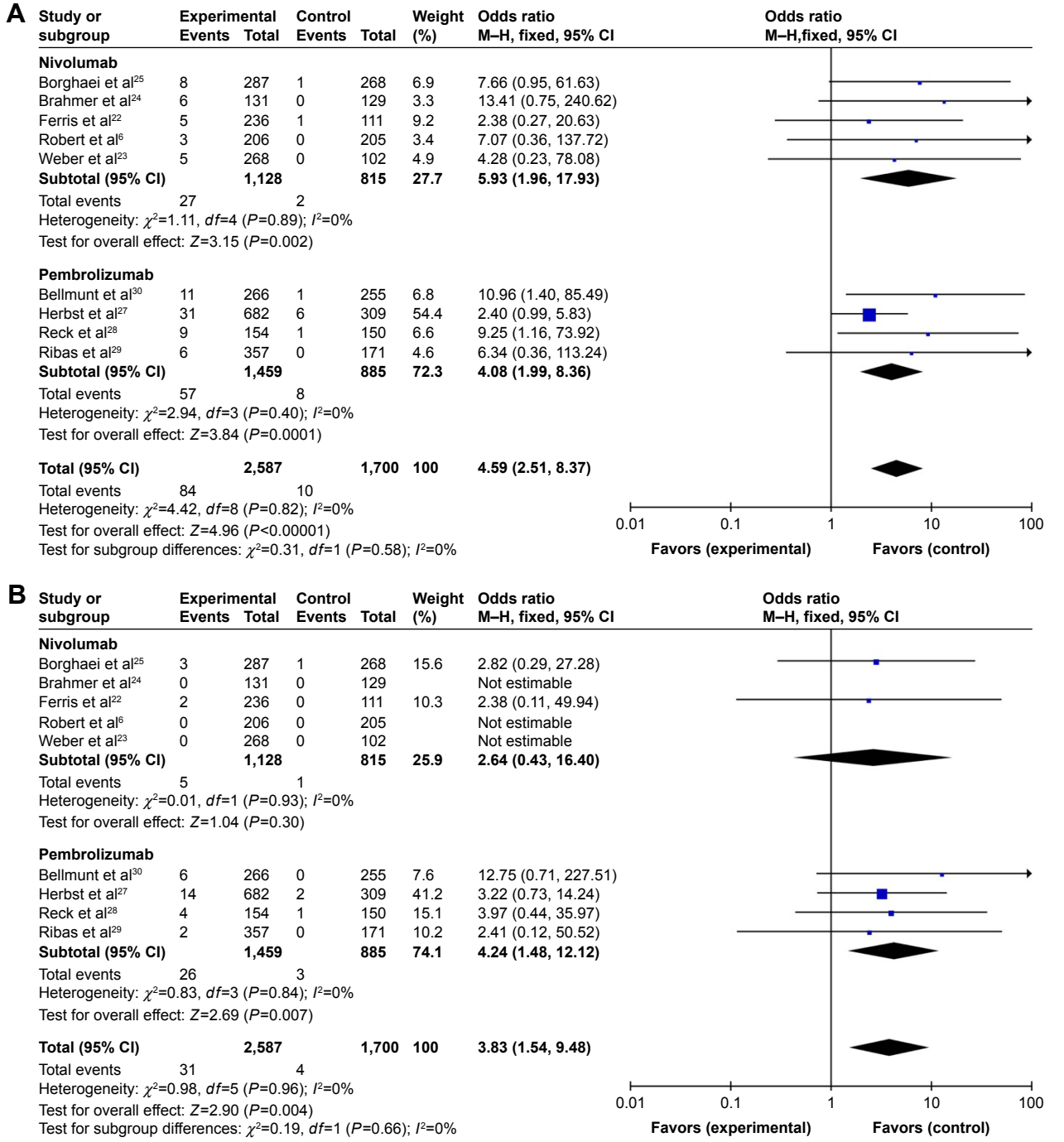

Figure 2 Forest plots for odds ratios for (**A**) all-grade and (**B**) high-grade pneumonitis for cancer patients receiving PD-1 inhibitors compared with controls (subgrouped by the type of drug used).

Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; PD-1, programmed cell death-1.

high-grade pneumonitis with nivolumab treatment was 2.64 (95% CI: 0.43–16.40; *P*=0.30) (Figure 2A and B).

Pembrolizumab

The OR for all-grade pneumonitis with pembrolizumab treatment was 4.08 (95% CI: 1.99–8.36; *P*=0.0001), and the OR for high-grade pneumonitis with pembrolizumab treatment was 4.24 (95% CI: 1.48–12.12; *P*=0.007) (Figure 2A and B). The dose of pembrolizumab utilized in the included studies varied, as some patients received 2 mg/kg every 3 weeks, while others received 10 mg/kg every 3 weeks or 200 mg every 3 weeks. Therefore, we also conducted a sub-analysis of studies reporting the incidences of all-grade and high-grade pneumonitis with treatment with pembrolizumab

monotherapy (subgrouped by the dose). The OR for all-grade pneumonitis with treatment with pembrolizumab at 2 mg/kg every 3 weeks was 2.84 (95% CI: 1.16–6.96; *P*=0.02), while the OR for all-grade pneumonitis with treatment with pembrolizumab at 10 mg/kg every 3 weeks was 2.65 (95% CI: 1.07–6.55; *P*=0.03), and that for high-grade pneumonitis with treatment with pembrolizumab at 10 mg/kg every 3 weeks was 3.52 (95% CI: 0.87–14.25; *P*=0.08). The OR for all-grade pneumonitis with treatment with pembrolizumab at 200 mg every 3 weeks was 10.11 (95% CI: 2.35–43.59; *P*=0.002), and the OR for high-grade pneumonitis with treatment with pembrolizumab at 200 mg every 3 weeks was 6.92 (95% CI: 1.24–38.55; *P*=0.03). We did not include studies reporting the incidence of high-grade pneumonitis with treatment with pembrolizumab at 2 mg/kg every 3 weeks in the subgroup analysis because these studies lacked a sufficient number of patients in both the 2 mg/kg Q3W group and the control group (Figure 3A and B). An additional funnel plot did not reveal evidence of publication bias (Figure 4).

To evaluate the ORs for pneumonitis-related death, we considered only studies comparing PD-1 inhibitors with a non-PD-1 inhibitor control. In addition, the study by

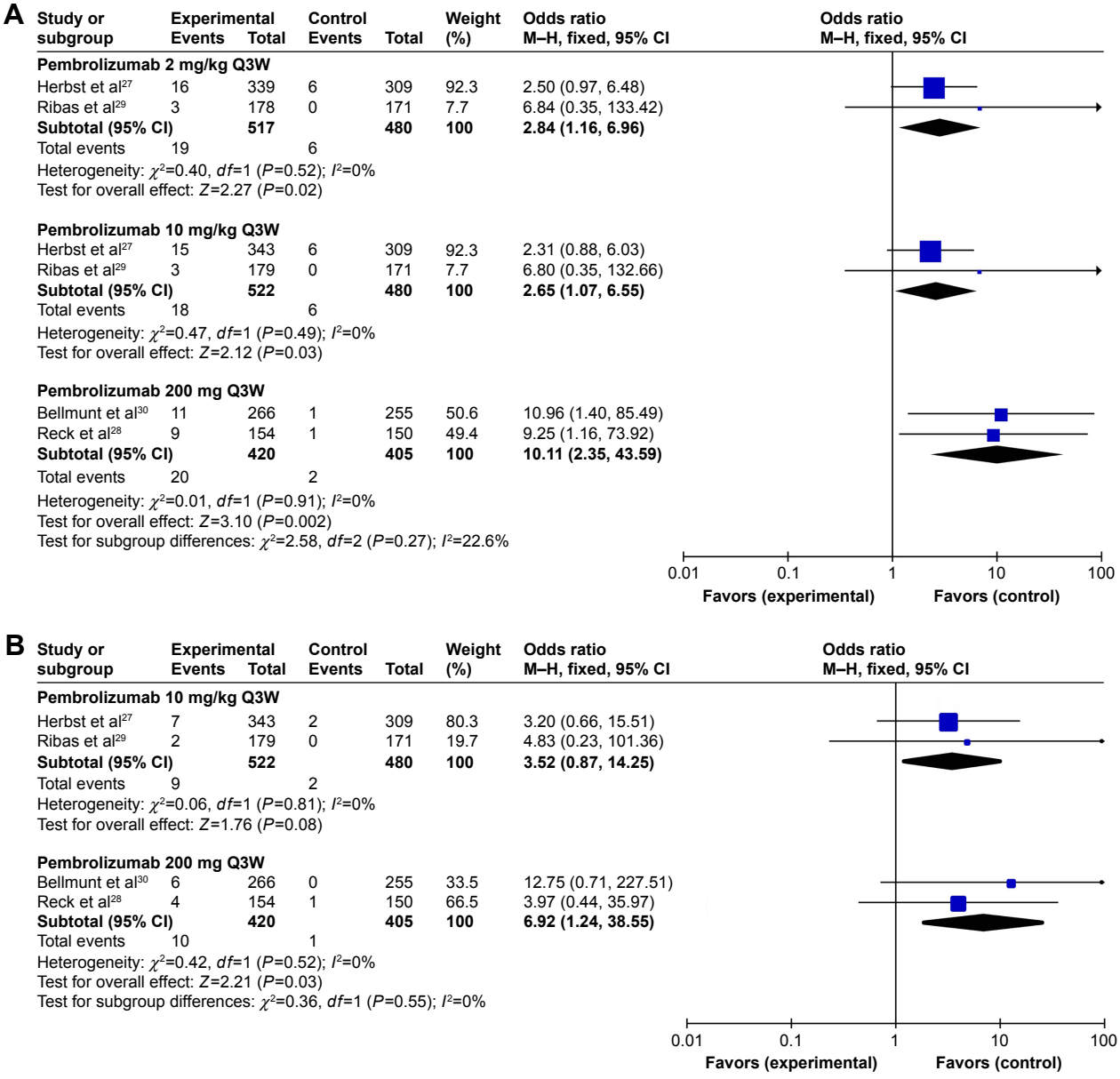

Figure 3 Forest plots for odds ratios for (**A**) all-grade and (**B**) high-grade pneumonitis for cancer patients receiving pembrolizumab compared with controls (subgrouped by the dose).

Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; Q3W, once every 3 weeks.

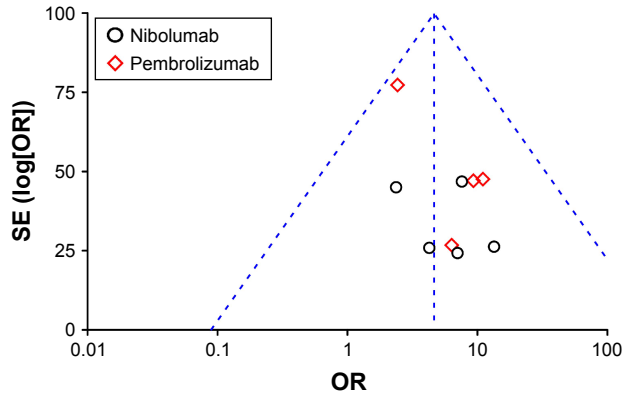

Figure 4 Funnel plot for publication bias.
Abbreviations: OR, odds ratio; SE, standard error.

Motzer et al[26] was excluded from the final analysis because it involved patients treated with everolimus, which is known to increase the risk of pneumonitis. The OR for pneumonitis-related death with treatment with PD-1 inhibitors was 2.47 (95% CI: 0.41–14.81; *P*=0.32) (Figure 5). We also conducted a separate analysis of four studies reporting the incidence of pneumonitis-related death with pembrolizumab monotherapy versus a control. The OR for pneumonitis-related death with pembrolizumab monotherapy versus a control was 3.06 (95% CI: 0.35–27.13; *P*=0.32) (Figure 6).

Other relevant comparisons

The OR for all-grade pneumonitis with nivolumab/ipilimumab combination therapy versus nivolumab monotherapy (evaluated in two studies)[31,32] was 3.54 (95% CI: 1.52–8.23; *P*=0.003), and the OR for high-grade pneumonitis with nivolumab/ipilimumab combination therapy versus nivolumab monotherapy was 2.35 (95% CI: 0.45–12.13; *P*=0.31) (Figure 7A and B).

Subgroup analysis

We conducted three different subgroup analyses to understand the effects of specific drug types, treatment regimens, and cancer types on the risk of treatment-related pneumonitis. When we compared subgroups according to the type of experimental drug with which patients were treated (nivolumab vs pembrolizumab), we noted no significant difference between the two subgroups with respect to the risk of pneumonitis (Figure 2A and B).

To evaluate the impact of dosage and therapy schedule on the risk of pneumonitis, we performed subgroup analysis of the pembrolizumab treatment groups according to the treatment regimens. Specifically, we compared the groups treated with 2 mg/kg pembrolizumab Q3 W with those treated with 10 mg/kg pembrolizumab Q3 W and those treated with 200 mg of pembrolizumab Q3 W. These results are presented in Figure 3A and B and showed that no significant difference existed among the subgroups with respect to the risk of all-grade pneumonitis or high-grade pneumonitis.

Since it is possible that certain types of cancers may predispose patients to developing pneumonitis (for example, NSCLC), we compared data pertaining to the effects of pembrolizumab treatment in NSCLC with those pertaining to the effects of pembrolizumab treatment in melanoma and other cancers. These results are presented in Figure 8A and B and showed that no significant difference existed among these subgroups with respect to the risk for all-grade pneumonitis or high-grade pneumonitis.

Discussion

The results of our analysis of 12 clinical trials including 6,240 cancer patients indicated that PD-1 inhibitors (nivolumab and pembrolizumab) were associated with a

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight (%)	Odds ratio M–H, fixed, 95% CI
Bellmunt et al[30]	1	266	0	255	27.2	2.89 (0.12, 71.20)
Borghaei et al[25]	0	287	0	268		Not estimable
Brahmer et al[24]	0	131	0	129		Not estimable
Ferris et al[22]	1	236	0	111	36.1	1.42 (0.06, 35.14)
Herbst et al[27]	3	682	0	309	36.7	3.19 (0.16, 61.91)
Reck et al[28]	0	154	0	150		Not estimable
Ribas et al[29]	0	357	0	171		Not estimable
Robert et al[6]	0	206	0	205		Not estimable
Weber et al[23]	0	268	0	102		Not estimable
Total (95% CI)		**2,587**		**1,700**	**100**	**2.47 (0.41, 14.81)**
Total events	5		0			

Heterogeneity: χ^2=0.15, *df*=2 (*P*=0.93); I^2=0%
Test for overall effect: *Z*=0.99 (*P*=0.32)

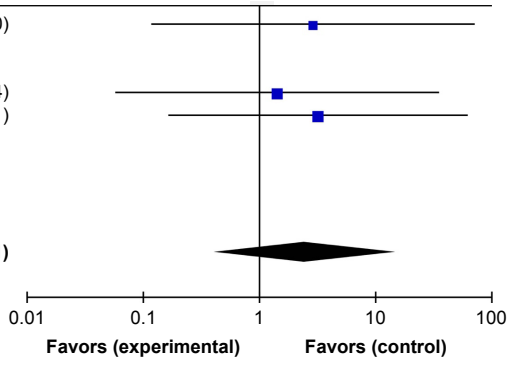

Figure 5 Forest plot for odds ratios for pneumonitis-related death in cancer patients receiving PD-1 inhibitors compared with controls.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; PD-1, programmed cell death-1.

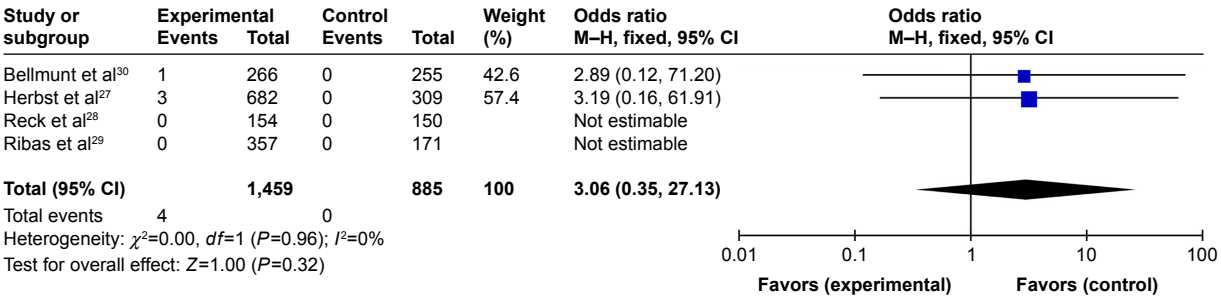

Figure 6 Forest plot for odds ratios for pneumonitis-related death in cancer patients receiving pembrolizumab compared with controls.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel.

higher risk of all-grade pneumonitis than control treatments. Pembrolizumab was associated with a higher risk of high-grade pneumonitis, whereas nivolumab was not. In all the included studies, the dose of nivolumab was 3 mg/kg body weight every 2 weeks, while the dose of pembrolizumab was 2 mg/kg body weight every 3 weeks, 10 mg/kg body weight every 3 weeks, or 200 mg every 3 weeks. Therefore, we conducted a subgroup analysis according to the drug regimen in case the dosage confounded our analysis. The analysis revealed that the risk of all-grade pneumonitis was higher with treatment with pembrolizumab, irrespective of the drug regimen, than with treatment with a control regimen, whereas the risk of high-grade pneumonitis was higher only with treatment with pembrolizumab at 200 mg every 3 weeks compared with treatment with a control regimen. However, given the small number of studies in this subgroup (two studies each), definitive conclusions cannot be made regarding the risk of pneumonitis associated with the above treatments. There was no significant difference in the OR for pneumonitis-related death between the group treated with PD-1 inhibitors and that treated with control regimens.

The risk of all-grade pneumonitis was higher with nivolumab/ipilimumab combination therapy than with nivolumab monotherapy. However, we noted no significant difference in the OR for high-grade pneumonitis between the group treated with nivolumab/ipilimumab combination therapy and that treated with nivolumab monotherapy. There was no significant difference in the OR for pneumonitis-related death between the group treated with a PD-1 inhibitor and that treated with a control regimen.

PD-1, the so-called "immune checkpoint", plays an important role in preventing T-cell activation; thus, it predominantly downregulates the immune system. PD-1 is expressed or upregulated in $CD4^+$ and $CD8^+$ T-cells, natural killer cells, B cells, monocytes, and dendritic cells during lymphocyte activation. It is also upregulated in certain tumors

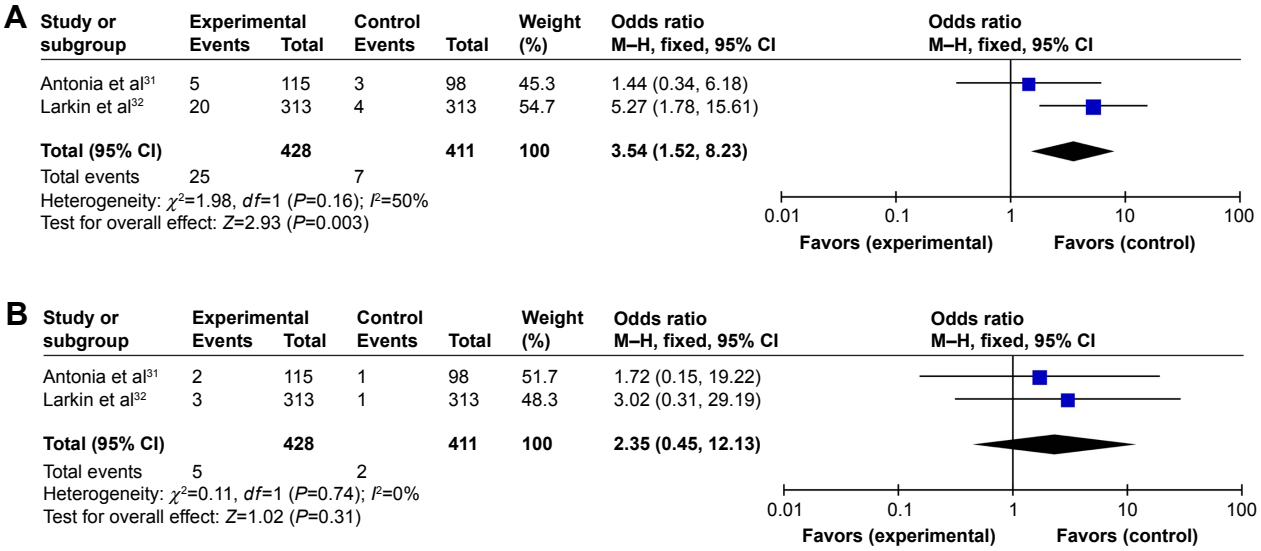

Figure 7 Forest plots for odds ratios for (**A**) all-grade and (**B**) high-grade pneumonitis for cancer patients receiving nivolumab/ipilimumab combination compared with patients receiving nivolumab monotherapy.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel.

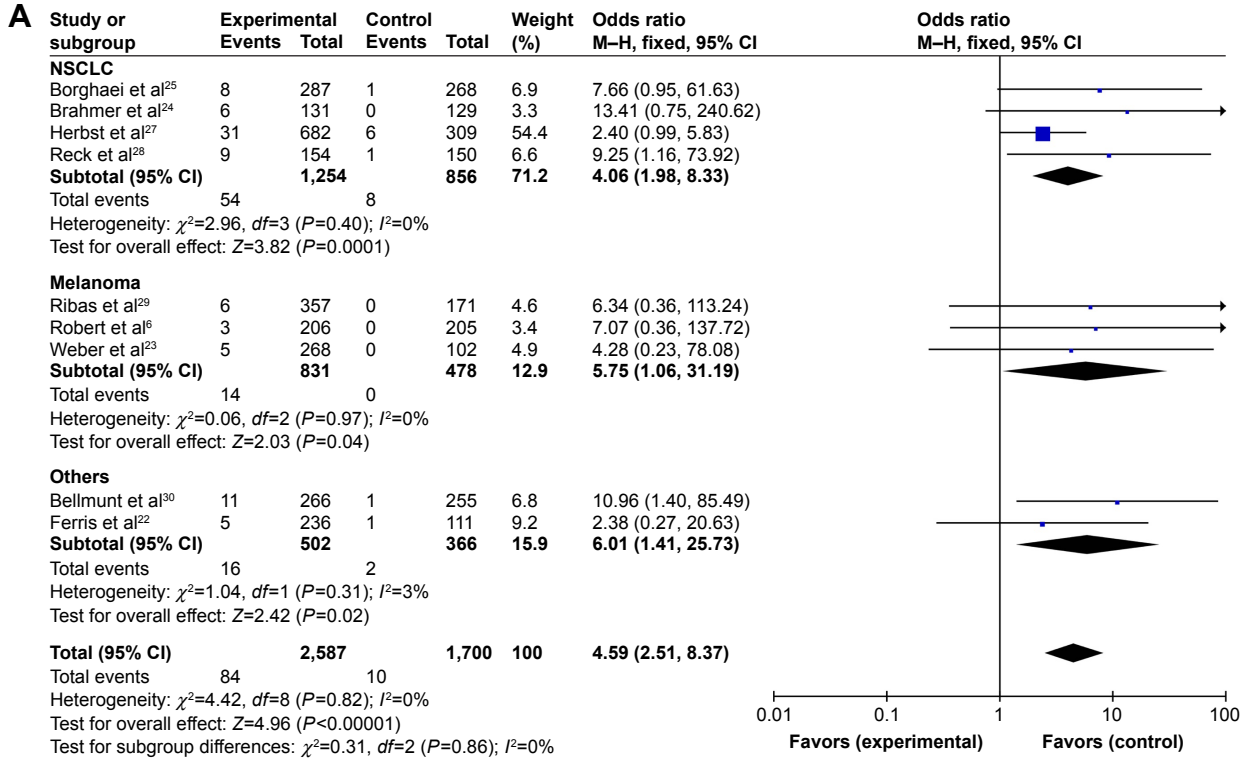

Figure 8 Forest plots for odds ratios for (**A**) all-grade and (**B**) high-grade pneumonitis for cancer patients receiving PD-1 inhibitors compared with controls (subgrouped by the treated cancer).

Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death-1.

and aids tumor cells in escaping immune surveillance.[33] Inhibiting PD-1 and its ligand (PD-L1) leads to enhanced T-cell action against cancer cells.[15] The anti-PD-1 antibodies pembrolizumab and nivolumab have been shown to have beneficial effects in several cancers.[6,22–30] Nivolumab and pembrolizumab were recently approved for use in patients with previously treated advanced NSCLC, and nivolumab has been approved for use in patients with previously treated

renal cell carcinoma.[7] Additionally, multiple ongoing Phase II and III studies are assessing the usefulness of these agents as treatments for many solid tumors and lymphomas.

In contrast to conventional chemotherapy, therapies that boost the immune system lead to a unique constellation of inflammatory toxicities known as IRAEs, whose development may require discontinuation of therapy and/or administration of immunosuppressive agents.[34,35] Among the IRAEs, pneumonitis, which has a morbidity of 3%, resulted in three treatment-related deaths in a Phase I trial of nivolumab as a treatment for NSCLC. These results increased the interest in the effects of drug treatments on the risk of pneumonitis among researchers.

Pneumonitis is a type of noninfectious lung inflammation characterized by interstitial and alveolar infiltration. Its clinical characteristics include dry, unproductive cough; tachypnea and dyspnea; tachycardia, cyanosis, and fatigue; and occasional fever and chills.[36] The presentation of pneumonitis is complicated and unpredictable, and the disease tends to occur later than other IRAEs. There are no criteria with which to differentiate drug-induced pneumonitis from other types of pneumonitis, nor are there criteria for assessing disease progression, which is important for determining treatment plans. Clinicians need to take the clinical symptoms and diagnostic findings characteristic of pneumonitis into account when planning treatment.

Pneumonitis is graded based on the severity of its associated radiographic alterations and clinical symptoms. Grade 1 pneumonitis presents as radiographic alterations without respiratory discomfort, whereas grade 2 pneumonitis is characterized by low-intensity clinical symptoms. Grade 3–4 pneumonitis causes severe clinical symptoms, such as dyspnea, cough, and hypoxia.

An early diagnosis, causative factor removal, and therapy initiation are essential for disease management. Immunosuppressive therapy should be guided by clinical responses, pulmonary function assessments, and radiographic imaging studies performed at 3-day intervals until improvement is observed.[37] In rare cases, additional immunosuppressive agents, such as azathioprine or cyclosporine, may be needed.[38] If squamous NSCLC is diagnosed early and treated adequately with nivolumab, the median time to resolution is short in affected patients.

The clinical symptoms and diagnostic findings characteristic of pneumonitis may be confounding factors with respect to differentiating between drug-induced pneumonitis development and disease progression. Careful multidisciplinary consultation should be conducted in each case of suspected pneumonitis to avoid improper disease management.

Potential correlations between the appearance of some treatment-related toxicities and responses to therapy were reported in previous studies. A study by Naidoo et al[39] showed that the majority of patients with pneumonitis were also responders to immunotherapy, irrespective of the primary disease, treatment regimen, or systems of assessment. However, these findings require confirmation in future studies.

One of the major limitations of our study was the absence of baseline comorbidity data, which may have confounded the analysis of the associations between the above treatments and the risks of pneumonitis and pneumonitis-related death. Thus, we could not establish whether potential additional risk factors, such as background lung disease, are associated with the development of pneumonitis. Individualized assessments of the risk of pneumonitis are thus indicated in clinical settings. In addition to the above limitation, the heterogeneity of the drugs and the doses used, as well as the cancer types treated, may also have weakened the results obtained herein. We attempted to overcome this limitation by performing subgroup analyses based on the cancer treated and the type of PD-1 inhibitor administered; however, these analyses revealed that there were no significant differences among the corresponding subgroups with respect to the risks of all-grade pneumonitis and high-grade pneumonitis.

Conclusion

Our analysis of the data demonstrated that the risk of all-grade pneumonitis was higher in patients treated with PD-1 inhibitors than in patients treated with control regimens, as well as in patients treated with nivolumab/ipilimumab combination therapy than in patients treated with nivolumab monotherapy. We also found that the risk of high-grade pneumonitis tended to be higher with treatment with pembrolizumab at a dose of 200 mg every 3 weeks than with treatment with control regimens. However, there was no significant difference between PD-1 inhibitors and control regimens with respect to the risk of pneumonitis-related death. Immune checkpoint inhibitors, especially those targeting PD-1, are among the most promising classes of emerging drugs, and we believe that our analysis adds to the body of data pertaining to their safety profile. Additional studies are needed to promote efficient disease management and patient care.

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Author contributions

All authors contributed to the data analysis and the drafting and revision of the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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