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ORIGINAL RESEARCH

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

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**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.<sup>1</sup> 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.<sup>2</sup> 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

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and metastatic settings.<sup>3,4</sup> 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).<sup>5–7</sup> 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.<sup>8</sup>

However, immune system activation is detrimental not only to the survival of cancer cells but also to certain types of healthy tissues.<sup>9</sup> 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.<sup>10-14</sup> 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.<sup>7,15,16</sup> 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.<sup>17,18</sup> 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.<sup>19</sup>

### 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 allgrade (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).<sup>20</sup> 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 I	Jadad	quality	assessment	of the	included studies
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Study	Randomization	Blinding	An account of	Overall
			all patients	score
Ferris et al <sup>22</sup>	2	0	I	3
Weber et al <sup>23</sup>	2	0	I	3
Robert et al <sup>6</sup>	2	2	I	5
Brahmer et al <sup>24</sup>	2	0	I	3
Borghaei et al <sup>25</sup>	2	0	I	3
Motzer et al <sup>26</sup>	2	0	I	3
Herbst et al <sup>27</sup>	2	0	I	3
Reck et al <sup>28</sup>	2	0	I	3
Ribas et al <sup>29</sup>	2	0	I	3
Bellmunt et al <sup>30</sup>	2	0	I	3
Antonia et al <sup>31</sup>	2	0	I	3
Larkin et al <sup>32</sup>	2	2	I	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.<sup>21</sup> 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<sup>23–26</sup> (one of which evaluated nivolumab vs everolimus),<sup>26</sup> four trials evaluated pembrolizumab,<sup>27–30</sup> and two trials compared nivolumab/ipilimumab combination therapy with nivolumab monotherapy.<sup>31,32</sup> 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

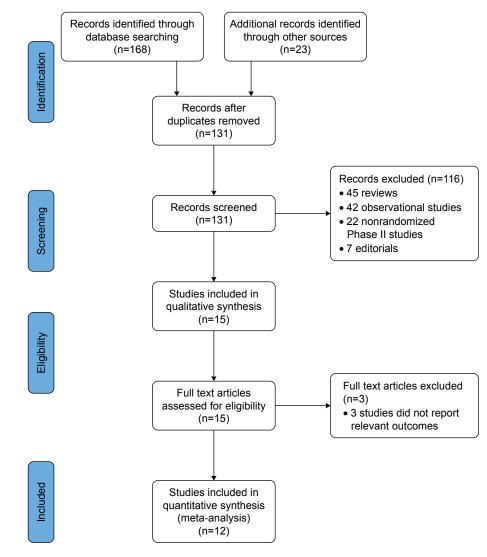


Figure I Flowchart of study selection.

Study	Study type	Treatment arms	Number of patients	Dose of the PD-I inhibitor	Indication	All-grade (grades 1–4) pneumonitis	High-grade (grades 3–4) pneumonitis	Pneumonitis- related death
Nivolumab studies Ferris et al <sup>22</sup>	Phase III	Arm A: nivolumab	Arm A: 236	Arm A: nivolumab	Squamous cell carcinoma	Arm A: 5 (2.1%)	Arm A: 2 (0.8%)	Arm A: 1 (0.4%)
Weber et al <sup>23</sup>	Phase III	Arm B: chemotherapy Arm A: nivolumab Arm B: chemotherapy	Arm B: 111 Arm A: 268 Arm B: 102	3 mg/kg Q2W Arm A: nivolumab 3 mg/kg Q2W	of the head and neck Melanoma	Arm B: I (0.9%) Arm A: 5 (1.9%) Arm B: 0 (0)	Arm B: 0 (0) Arm A: 0 (0) Arm B: 0 (0)	Arm B: 0 (0) Arm A: 0 (0) Arm B: 0 (0)
Robert et al <sup>6</sup>	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 <sup>24</sup>	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 <sup>25</sup>	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: I (<1%)	Arm A: 0 (0) Arm B: 0 (0)
Motzer et al <sup>26</sup>	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 <sup>27</sup>	Phase III	Arm A: pembrolizumab Arm B: pembrolizumab	Arm A: 339 Arm B: 343	Arm A: pembrolizumab 2 mg/kg O3VV	Advanced non-small-cell lung cancer	Arm A: 16 (5%) Arm B: 15 (4%)	Arm A: 7 (2%) Arm B: 7 (2%)	Arm A: 2 (0.6%) Arm B: 1 (0.3%)
		Arm C: docetaxel	Arm C: 309	Arm B: pembrolizumab 10 mg/kg Q3W	5	Arm C: 6 (2%)	Arm C: 2 (1%)	Arm C: 0 (0)
Reck et al <sup>28</sup>	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: I (0.7%)	Arm A: 0 (0) Arm B: 0 (0)
Ribas et al <sup>29</sup>	Phase II	Arm A: pembrolizumab Arm B: pembrolizumab	Arm A: 178 Arm B: 179	Arm A: pembrolizumab 2 mg/kg Q3W	Melanoma	Arm A: 3 (2%) Arm B: 3 (2%)	Arm A: 0 (0) Arm B: 2 (1%)	Arm A: 0 (0) Arm B: 0 (0)
		Arm C: cnemotnerapy		Arm B: pemorolizumad 10 mg/kg Q3W				Arm C: 0 (0)
Bellmunt et al <sup>30</sup>	Phase III	Arm A: pembrolizumab Arm B: chemotherapy	Arm A: 266 Arm B: 255	Arm A: pembrolizumab 200 mg O3W	Advanced urothelial carcinoma	Arm A: 11 (4.1%) Arm B: 1 (0.4%)	Arm A: 6 (2.3%) Arm B: 0 (0)	Arm A: I (0.4%) Arm B: 0 (0)

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Study	Study type	Treatment arms	Number of patients	Dose of the PD-I inhibitor	Indication	All-grade (grades I–4) pneumonitis	High-grade (grades 3–4) pneumonitis	Pneumonitis- related death
Antonia	Phase II	Arm A: nivolumab	Arm A: 98	Arm A: nivolumab	Recurrent	Arm A: 3 (3%)	Arm A: I (I%)	Arm A: 0 (0)
et al <sup>31</sup>		Arm B: nivolumab	Arm B: 61	3 mg/kg Q2W	small-cell	Arm B: 2 (4%)	Arm B: I (2%)	Arm B: 0 (0)
		plus ipilimumab Arm C: nivolumab plus ipilimumab	Arm C: 54	Arm B: nivolumab I mg/kg plus ipilimumab 3 mg/kg Q3W Arm C: nivolumab 3 mg/kg plus ipilimumab I mg/kg Q3W	lung cancer	Arm C: 3 (6%)	Arm C: I (2%)	Arm C: 0 (0)
Larkin et al <sup>32</sup>	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: I (0.3%) Arm B: 3 (1%) Arm C: I (0.3%)	Arm A: 0 (0) Arm B: 0 (0) Arm C: 0 (0)

Table 3 Direct comparison of different PD-1 inhibitors

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 (allgrade 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<sup>26</sup> 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

A Study or subgroup	Experin Events		Control Events		Weight (%)	Odds ratio M–H, fixed, 95% C	I	Odds ratio M–H,fixed,	95% CI	
Nivolumab										
Borghaei et al <sup>25</sup>	8	287	1	268	6.9	7.66 (0.95, 61.63)				_
Brahmer et al <sup>24</sup>	6	131	0	129	3.3	13.41 (0.75, 240.62	)	+		
Ferris et al <sup>22</sup>	5	236	1	111	9.2	2.38 (0.27, 20.63)				
Robert et al6	3	206	0	205	3.4	7.07 (0.36, 137.72)				<b>→</b>
Weber et al <sup>23</sup>	5	268	0	102	4.9	4.28 (0.23, 78.08)				
Subtotal (95% CI)		1,128		815	27.7	5.93 (1.96, 17.93)				
Total events	27		2							
Heterogeneity: $\chi^{2=1}$ Test for overall effe				I						
Pembrolizumab			,							
Bellmunt et al <sup>30</sup>	11	266	1	255	6.8	10.96 (1.40, 85.49)				
Herbst et al27	31	682	6	309	54.4	2.40 (0.99, 5.83)				
Reck et al <sup>28</sup>	9	154	1	150	6.6	9.25 (1.16, 73.92)		-		
Ribas et al <sup>29</sup>	6	357	0	171	4.6	6.34 (0.36, 113.24)				<b>→</b>
Subtotal (95% CI)		1,459		885	72.3	4.08 (1.99, 8.36)			•	
Total events	57	,	8			,				
Heterogeneity: $\chi^2$ =2 Test for overall effe	2.94, <i>df=</i> 3	-	40); /²=0%	)						
Total (95% CI)		2,587		1,700	100	4.59 (2.51, 8.37)			•	
Total events	84 142 df-6	<u>م</u> _م (	10				L		1	
Heterogeneity: $\chi^2 = 4$		-		)			0.01	0.1 1	10	1(
Test for overall effe										
Test for subgroup d	ifferences	$\chi^2 = 0.3$	31, <i>df</i> =1 (	P=0.58)	; /2=0%		Favors	(experimental)	Favors (control)	
_										
B Study or subgroup	Experin Events		Control Events		Weight (%)	Odds ratio M–H, fixed, 95% C	I	Odds ratio M–H, fixed,	95% CI	
subgroup					•		I		95% CI	
subgroup Nivolumab	Events	Total	Events	Total	(%)	M–H, fixed, 95% C	I		95% Cl	
subgroup Nivolumab Borghaei et al <sup>25</sup>	Events 3	<b>Total</b> 287	Events	Total	•	M–H, fixed, 95% C 2.82 (0.29, 27.28)	l		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup>	Events 3 0	<b>Total</b> 287 131	Events 1 0	<b>Total</b> 268 129	(%) 15.6	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable	I		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup>	<b>Events</b> 3 0 2	<b>Total</b> 287 131 236	<b>Events</b> 1 0 0	<b>Total</b> 268 129 111	(%)	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94)	I		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup>	<b>Events</b> 3 0 2 0	<b>Total</b> 287 131 236 206	<b>Events</b> 1 0 0 0	<b>Total</b> 268 129 111 205	(%) 15.6	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable	I		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup>	<b>Events</b> 3 0 2	<b>Total</b> 287 131 236 206 268	<b>Events</b> 1 0 0	<b>Total</b> 268 129 111 205 102	(%) 15.6 10.3	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable	1		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup>	<b>Events</b> 3 0 2 0	<b>Total</b> 287 131 236 206	<b>Events</b> 1 0 0 0	<b>Total</b> 268 129 111 205	(%) 15.6	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable	ı <u> </u>		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup>	<b>Events</b> 3 0 2 0 0 0 5 0.01, <i>df=</i> 1	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5	Events 1 0 0 0 0 1 93); I <sup>2</sup> =0%	<b>Total</b> 268 129 111 205 102 <b>815</b>	(%) 15.6 10.3	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable	1		95% CI	
subgroupNivolumabBorghaei et al25Brahmer et al24Ferris et al22Robert et al6Weber et al23Subtotal (95% CI)Total eventsHeterogeneity: $\chi^2$ =0	<b>Events</b> 3 0 2 0 0 0 5 0.01, <i>df=</i> 1	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5	Events 1 0 0 0 0 1 93); I <sup>2</sup> =0%	<b>Total</b> 268 129 111 205 102 <b>815</b>	(%) 15.6 10.3	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable	<u>.</u>		95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup> Subtotal (95% CI) Total events Heterogeneity: $\chi^2$ =( Test for overall effe	<b>Events</b> 3 0 2 0 0 0 5 0.01, <i>df=</i> 1	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5	Events 1 0 0 0 0 1 93); I <sup>2</sup> =0%	<b>Total</b> 268 129 111 205 102 <b>815</b>	(%) 15.6 10.3	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable			95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup> Subtotal (95% Cl) Total events Heterogeneity: $\chi^2$ =( Test for overall effe Pembrolizumab	3 0 2 0 0 0 5 0.01, <i>df=</i> <sup>-</sup> ct: <i>Z</i> =1.04	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5 4 ( <i>P</i> =0.5	Events 1 0 0 0 0 1 1 0 3 ); l <sup>2</sup> =0%	<b>Total</b> 268 129 111 205 102 <b>815</b>	(%) 15.6 10.3 <b>25.9</b>	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable 2.64 (0.43, 16.40)			95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup> Subtotal (95% Cl) Total events Heterogeneity: $\chi^2$ =( Test for overall effe Pembrolizumab Bellmunt et al <sup>30</sup>	3 0 2 0 0 0 5 5 0.01, df=1 6	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5 4 ( <i>P</i> =0.5) 266	Events 1 0 0 0 1 33); l <sup>2</sup> =0% 30) 0	Total 268 129 111 205 102 <b>815</b> 255	(%) 15.6 10.3 <b>25.9</b> 7.6	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable 2.64 (0.43, 16.40)			95% CI	
subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup> Subtotal (95% Cl) Total events Heterogeneity: <i>x</i> <sup>2</sup> =( Test for overall effe Pembrolizumab Bellmunt et al <sup>30</sup> Herbst et al <sup>27</sup>	<b>Events</b> 3 0 2 0 0 5 0.01, <i>df=</i> 1.04 6 14	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5 4 ( <i>P</i> =0.5 266 682	Events 1 0 0 0 1 33); l <sup>2</sup> =0% 30) 0 2	Total 268 129 111 205 102 <b>815</b> 255 309	(%) 15.6 10.3 <b>25.9</b> 7.6 41.2	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable Not estimable 2.64 (0.43, 16.40) 12.75 (0.71, 227.51 3.22 (0.73, 14.24)			95% CI	
subgroup         Nivolumab         Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup> Subtotal (95% Cl)         Total events         Heterogeneity: χ <sup>2</sup> =         Test for overall effe         Pembrolizumab         Bellmunt et al <sup>30</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Ribas et al <sup>29</sup>	Events           3           0           2           0           5           0.01, df=1           ct: Z=1.04           6           14           4	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5 4 ( <i>P</i> =0.5) 4 ( <i>P</i> =0.5) 266 682 154 357	Events 1 0 0 0 0 33); l <sup>2</sup> =0% 30) 0 2 1	Total 268 129 111 205 102 <b>815</b> 255 309 150	(%) 15.6 10.3 <b>25.9</b> 7.6 41.2 15.1	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable 2.64 (0.43, 16.40) 12.75 (0.71, 227.51 3.22 (0.73, 14.24) 3.97 (0.44, 35.97) 2.41 (0.12, 50.52)			95% CI	
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subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>8</sup> Weber et al <sup>23</sup> Subtotal (95% CI) Total events Heterogeneity: $\chi^{2=\ell}$ Test for overall effe Pembrolizumab Bellmunt et al <sup>30</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Ribas et al <sup>29</sup> Subtotal (95% CI) Total events Heterogeneity: $\chi^{2=\ell}$	Events           3           0           2           0           5           0.01, df='           5           14           4           2           0.83, df=3	<b>Total</b> 287 131 236 206 268 <b>1,128</b> 1 ( <i>P</i> =0.5 4 ( <i>P</i> =0.5 4 ( <i>P</i> =0.5 57 <b>1,459</b> 3 ( <i>P</i> =0.5	Events 1 0 0 0 1 1 0 3 1 0 3 3 3 1 1 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 268 129 111 205 102 <b>815</b> 255 309 150 171 <b>885</b>	(%) 15.6 10.3 <b>25.9</b> 7.6 41.2 15.1 10.2 <b>74.1</b>	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable 2.64 (0.43, 16.40) 12.75 (0.71, 227.51 3.22 (0.73, 14.24) 3.97 (0.44, 35.97) 2.41 (0.12, 50.52)			95% CI	
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subgroup Nivolumab Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Ferris et al <sup>22</sup> Robert et al <sup>6</sup> Weber et al <sup>23</sup> Subtotal (95% Cl) Total events Heterogeneity: $\chi^2$ =1 Pembrolizumab Bellmunt et al <sup>20</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Ribas et al <sup>29</sup> Subtotal (95% Cl) Total events Heterogeneity: $\chi^2$ =1 Test for overall effe Total (95% Cl) Total events	Events           3           0           2           0           5           0.01, df='           ct: Z=1.04           6           14           4           2           0.83, df=3           ct: Z=2.69           31           0.98, df=5           ct: Z=2.90	Total 287 131 236 206 268 1,128 1 (P=0.5 4 (P=0.5 266 682 154 357 1,459 8 (P=0.6 9 (P=0.6 2,587 5 (P=0.5 0 (P=0.6) 9 (P=0.6) 1 (P=0.5) 1 (P=0.5)	Events 1 0 0 0 1 1 0 3 3 3 3 3 1 0 0 2 1 0 0 3 3 3 3 3 3 3 3 3 3 3 3 3	Total 268 129 111 205 102 815 255 309 150 171 885 1,700	(%) 15.6 10.3 25.9 7.6 41.2 15.1 10.2 74.1 100	M–H, fixed, 95% C 2.82 (0.29, 27.28) Not estimable 2.38 (0.11, 49.94) Not estimable 2.64 (0.43, 16.40) 12.75 (0.71, 227.51 3.22 (0.73, 14.24) 3.97 (0.44, 35.97) 2.41 (0.12, 50.52) 4.24 (1.48, 12.12)	) 0.01		95% CI	

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

Abbreviations: Cl, 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

Α	Study or subgroup	Experin Events	nental Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl	
	Pembrolizumat	o 2 mg/kg	Q3W						
	Herbst et al27	16	339	6	309	92.3	2.50 (0.97, 6.48)	<b></b>	
	Ribas et al <sup>29</sup>	3	178	0	171	7.7	6.84 (0.35, 133.42)		
	Subtotal (95% 0		517		480	100	2.84 (1.16, 6.96)		
	Total events	19		6					
	Heterogeneity: $\chi$ Test for overall e				)				
	Pembrolizumat	o 10 ma/ka	a Q3W						
	Herbst et al27	15	343	6	309	92.3	2.31 (0.88, 6.03)		
	Ribas et al29	3	179	0	171	7.7	6.80 (0.35, 132.66)		
	Subtotal (95% 0	CI)	522		480	100	2.65 (1.07, 6.55)		
	Total events	18		6				-	
	Heterogeneity: $\chi$ Test for overall e				)				
	Pembrolizumat	o 200 ma (	23W						
	Bellmunt et al <sup>30</sup>	11	266	1	255	50.6	10.96 (1.40, 85.49)		
	Reck et al <sup>28</sup>	9	154	1	150	49.4	9.25 (1.16, 73.92)		
	Subtotal (95% 0	-	420	•	405	100	10.11 (2.35, 43.59)		
	•••••••	,		2					
	Total events Heterogeneity: χ Test for overall e			.91); /²=0%	)				
		2=0.01, <i>df</i> effect: Z=3.	.10 (P=0	.91); /²=0% .002)		; /²=22.6%	0.01	0.1 1 10 's (experimental) Favors (con	
в	Heterogeneity: χ Test for overall e	2=0.01, <i>df</i> effect: Z=3.	.10 ( <i>P</i> =0 es: χ²=2	.91); /²=0% .002)		; /²=22.6% Weight (%)	0.01		
в	Heterogeneity: $\chi$ Test for overall e Test for subgrou Study or	2 <sup>2</sup> =0.01, <i>df</i> effect: Z=3. p difference Experim Events	10 (P=0 ees: $\chi^2=2$ nental Total	.91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 ( <b>Control</b>	P=0.27)	Weight	0.01 Favoi Odds ratio	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrou Study or subgroup	2 <sup>2</sup> =0.01, <i>df</i> effect: Z=3. p difference Experim Events	10 (P=0 ees: $\chi^2=2$ nental Total	.91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 ( <b>Control</b>	P=0.27)	Weight	0.01 Favoi Odds ratio	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrou Study or subgroup Pembrolizumat	2 <sup>2</sup> =0.01, <i>df</i> effect: Z=3. p difference Experim Events p 10 mg/kg	$\frac{10}{(P=0)}$ $\frac{10}{\chi^2=2}$ $\frac{1}{\chi^2=2}$ $\frac{1}{\chi^2=2}$	.91); /²=0% .002) .58, <i>df</i> =2 ( Control Events	P=0.27) Total	Weight (%)	0.01 Favor Odds ratio M–H, fixed, 95% Cl	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrou Study or subgroup Pembrolizumat Herbst et al <sup>27</sup>	2 <sup>2</sup> =0.01, <i>df</i> fffect: <i>Z</i> =3. p difference <b>Experim</b> <b>Events</b> <b>5 10 mg/kg</b> 7 2	$\frac{10}{(P=0)}$ $\frac{10}{\chi^2=2}$ $\frac{1}{\chi^2=2}$ $\frac{1}{\chi^2=2}$ $\frac{1}{\chi^2=2}$ $\frac{1}{\chi^2=2}$	91); /²=0% .002) .58, df=2 ( Control Events	P=0.27) Total 309	Weight (%) 80.3	0.01 Favor Odds ratio M–H, fixed, 95% CI 3.20 (0.66, 15.51)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrou Study or subgroup Pembrolizumat Herbst et al <sup>27</sup> Ribas et al <sup>29</sup>	2 <sup>2</sup> =0.01, <i>df</i> fffect: <i>Z</i> =3. p difference <b>Experim</b> <b>Events</b> <b>5 10 mg/kg</b> 7 2	.10 ( <i>P</i> =0 ces: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179	91); /²=0% .002) .58, df=2 ( Control Events	P=0.27) Total 309 171	<b>Weight</b> (%) 80.3 19.7	0.01 Favor Odds ratio M–H, fixed, 95% Cl 3.20 (0.66, 15.51) 4.83 (0.23, 101.36)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrout Study or subgroup Pembrolizumat Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C	2 <sup>2</sup> =0.01, <i>df</i> effect: <i>Z</i> =3. p difference <b>Experim</b> Events o 10 mg/kg 7 2 Cl) 9	10 (P=0 ces: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179 <b>522</b>	91); /²=0% .002) .58, df=2 ( Control Events 2 0 2	P=0.27) Total 309 171 480	<b>Weight</b> (%) 80.3 19.7	0.01 Favor Odds ratio M–H, fixed, 95% Cl 3.20 (0.66, 15.51) 4.83 (0.23, 101.36)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrout Study or subgroup Pembrolizumat Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events	2 <sup>2</sup> =0.01, <i>df</i> effect: <i>Z</i> =3. p difference <b>Experim</b> <b>Events</b> <b>5 10 mg/kg</b> 7 2 <b>CI)</b> 9 9 2 <sup>2</sup> =0.06, <i>df</i>	10 (P=0 es: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179 <b>522</b> <i>f</i> =1 (P=0	.91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 ( <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0%	P=0.27) Total 309 171 480	<b>Weight</b> (%) 80.3 19.7	0.01 Favor Odds ratio M–H, fixed, 95% Cl 3.20 (0.66, 15.51) 4.83 (0.23, 101.36)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrout Study or subgroup Pembrolizumati Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumati	2 <sup>2</sup> =0.01, <i>df</i> fffect: <i>Z</i> =3. p difference Experim Events 5 10 mg/kg 7 2 CI) 9 2 <sup>2</sup> =0.06, <i>df</i> effect: <i>Z</i> =1. 5 200 mg (0)	10 (P=0 es: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179 <b>522</b> =1 (P=0 76 (P=0)	.91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08)	P=0.27) Total 309 171 480	Weight (%) 80.3 19.7 100	0.01 Favor Odds ratio M–H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrout Study or subgroup Pembrolizumat Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumat Bellmunt et al <sup>30</sup>	$z^{2}=0.01, df$ effect: Z=3. p difference Experim Events o 10 mg/kg 7 2 CI) 9 $y^{2}=0.06, df$ effect: Z=1. o 200 mg ( $6$	10 (P=0 bes: $\chi^{2}=2$ <b>nental</b> Total <b>g Q3W</b> 343 179 522 <i>f=</i> 1 (P=0 76 (P=0 <b>Q3W</b> 266	91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08) 0	P=0.27) Total 309 171 480 255	Weight (%) 80.3 19.7 100 33.5	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subground Study or subgroup Pembrolizumate Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% O Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumate Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup>	$z^2=0.01, df$ effect: Z=3. p difference Experim Events o 10 mg/kg 7 2 CI) 9 $z^2=0.06, df$ effect: Z=1. o 200 mg ( 6 4	10 (P=0 es: χ <sup>2</sup> =2 mental Total g Q3W 343 179 522 5=1 (P=0 76 (P=0 23W 266 154	.91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08)	P=0.27) Total 309 171 480 255 150	Weight (%) 80.3 19.7 100 33.5 66.5	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25) 12.75 (0.71, 227.51) 3.97 (0.44, 35.97)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgroup Pembrolizumat Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumat Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup> Subtotal (95% C	$z^2=0.01, df$ effect: Z=3. p difference Experime Events o 10 mg/kg 7 2 CI) 9 $z^2=0.06, df$ effect: Z=1. o 200 mg ( 6 4 CI)	10 (P=0 bes: $\chi^{2}=2$ <b>nental</b> Total <b>g Q3W</b> 343 179 522 <i>f=</i> 1 (P=0 76 (P=0 <b>Q3W</b> 266	91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08) 0	P=0.27) Total 309 171 480 255	Weight (%) 80.3 19.7 100 33.5	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgroup Pembrolizumat Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumat Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup> Cubtal (95% C Total events	$y^2=0.01, df$ effect: Z=3. p difference Experime Events p 10 mg/kg 7 2 CI) 9 $y^2=0.06, df$ effect: Z=1. p 200 mg ( 6 4 CI) 10	10 (P=0 es: χ <sup>2</sup> =2 hental Total 9 Q3W 343 179 522 f=1 (P=0 76 (P=0 266 154 420	.91); /²=0% .002) .58, df=2 (. <b>Control Events</b> 2 0 2.81); /²=0% .08) 0 1 1	P=0.27) Total 309 171 480 255 150 405	Weight (%) 80.3 19.7 100 33.5 66.5	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25) 12.75 (0.71, 227.51) 3.97 (0.44, 35.97)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrout Study or subgroup Pembrolizumate Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumate Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup> Subtotal (95% C Total events Heterogeneity: $\chi$	$z^{2}=0.01, df$ effect: Z=3. p difference Experim Events 5 10 mg/kg 7 2 CI) 9 $z^{2}=0.06, df$ effect: Z=1. 5 200 mg ( 6 4 CI) 10 $z^{2}=0.42, df$	10 (P=0 es: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>Q3W</b> <b>343</b> 179 <b>522</b> <b>5</b> =1 (P=0 <b>Q3W</b> 266 154 <b>420</b> <b>5</b> =1 (P=0) <b>2</b> =1 (P=0) <b>3</b> =1	.91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% 0 1 1 .52); <i>I</i> <sup>2</sup> =0%	P=0.27) Total 309 171 480 255 150 405	Weight (%) 80.3 19.7 100 33.5 66.5	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25) 12.75 (0.71, 227.51) 3.97 (0.44, 35.97)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgroup Subgroup Pembrolizumate Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumate Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e	$z^2=0.01, df$ effect: Z=3. p difference Experim Events 5 10 mg/kg 7 2 CI) 9 $y^2=0.06, df$ effect: Z=1. 5 200 mg ( 6 4 CI) 10 $y^2=0.42, df$ effect: Z=2.	10 (P=0 es: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179 <b>522</b> 5=1 (P=0 <b>23W</b> 266 154 <b>420</b> 5=1 (P=0 21 (P=0 21 (P=0) 21 (P=0) 22 (P=0) 21 (P=	91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08) 0 1 .52); <i>I</i> <sup>2</sup> =0% .03)	P=0.27) Total 309 171 480 255 150 405	Weight (%) 80.3 19.7 100 33.5 66.5 100	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25) 12.75 (0.71, 227.51) 3.97 (0.44, 35.97)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgrout Study or subgroup Pembrolizumate Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumate Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup> Subtotal (95% C Total events Heterogeneity: $\chi$	$z^2=0.01, df$ effect: Z=3. p difference Experim Events 5 10 mg/kg 7 2 CI) 9 $y^2=0.06, df$ effect: Z=1. 5 200 mg ( 6 4 CI) 10 $y^2=0.42, df$ effect: Z=2.	10 (P=0 es: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179 <b>522</b> 5=1 (P=0 <b>23W</b> 266 154 <b>420</b> 5=1 (P=0 21 (P=0 21 (P=0) 21 (P=0) 22 (P=0) 21 (P=	91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08) 0 1 .52); <i>I</i> <sup>2</sup> =0% .03)	P=0.27) Total 309 171 480 255 150 405	Weight (%) 80.3 19.7 100 33.5 66.5 100	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25) 12.75 (0.71, 227.51) 3.97 (0.44, 35.97)	rs (experimental) Favors (con Odds ratio	
в	Heterogeneity: $\chi$ Test for overall e Test for subgroup Subgroup Pembrolizumate Herbst et al <sup>27</sup> Ribas et al <sup>29</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e Pembrolizumate Bellmunt et al <sup>30</sup> Reck et al <sup>28</sup> Subtotal (95% C Total events Heterogeneity: $\chi$ Test for overall e	$z^2=0.01, df$ effect: Z=3. p difference Experim Events 5 10 mg/kg 7 2 CI) 9 $y^2=0.06, df$ effect: Z=1. 5 200 mg ( 6 4 CI) 10 $y^2=0.42, df$ effect: Z=2.	10 (P=0 es: χ <sup>2</sup> =2 <b>nental</b> <b>Total</b> <b>g Q3W</b> 343 179 <b>522</b> 5=1 (P=0 <b>23W</b> 266 154 <b>420</b> 5=1 (P=0 21 (P=0 21 (P=0) 21 (P=0) 22 (P=0) 21 (P=	91); <i>I</i> <sup>2</sup> =0% .002) .58, <i>df</i> =2 (. <b>Control</b> <b>Events</b> 2 0 2 .81); <i>I</i> <sup>2</sup> =0% .08) 0 1 .52); <i>I</i> <sup>2</sup> =0% .03)	P=0.27) Total 309 171 480 255 150 405	Weight (%) 80.3 19.7 100 33.5 66.5 100	0.01 Favor Odds ratio M-H, fixed, 95% CI 3.20 (0.66, 15.51) 4.83 (0.23, 101.36) 3.52 (0.87, 14.25) 12.75 (0.71, 227.51) 3.97 (0.44, 35.97)	rs (experimental) Favors (con Odds ratio	

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.

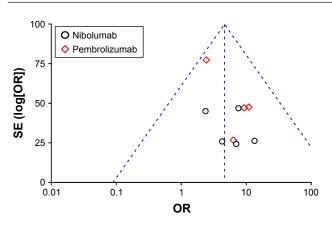


Figure 4 Funnel plot for publication bias. Abbreviations: OR, odds ratio; SE, standard error.

Motzer et al<sup>26</sup> 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 pneumonitisrelated 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)<sup>31,32</sup> 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

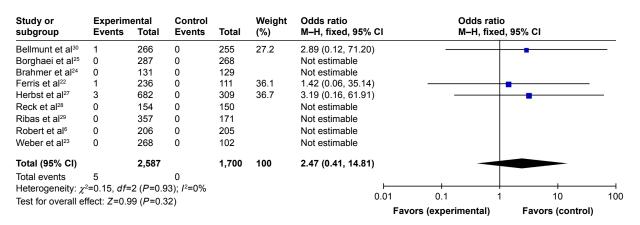


Figure 5 Forest plot for odds ratios for pneumonitis-related death in cancer patients receiving PD-1 inhibitors compared with controls. Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; PD-1, programmed cell death-1.

Study or subgroup	Experim Events	ental Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed,	95% CI	
Bellmunt et al <sup>30</sup> Herbst et al <sup>27</sup>	1	266	0	255	42.6	2.89 (0.12, 71.20)		•	_
Reck et al <sup>28</sup>	3 0	682 154	0 0	309 150	57.4	3.19 (0.16, 61.91) Not estimable			-
Ribas et al <sup>29</sup>	0	357	0	171		Not estimable			
Total (95% CI)		1,459		885	100	3.06 (0.35, 27.13)			
Total events Heterogeneity: $\chi$ Test for overall e		•				0.01 Favor	0.1 1 s (experimental)	10 Favors (control)	

Figure 6 Forest plot for odds ratios for pneumonitis-related death in cancer patients receiving pembrolizumab compared with controls. Abbreviations: Cl, 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 highgrade 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 pneumonitisrelated 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<sup>+</sup> and CD8<sup>+</sup> T-cells, natural killer cells, B cells, monocytes, and dendritic cells during lymphocyte activation. It is also upregulated in certain tumors

Α	Study or subgroup	Experim Events	ental Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl	
	Antonia et al <sup>31</sup>	5	115	3	98	45.3	1.44 (0.34, 6.18)	<b></b>	
	Larkin et al32	20	313	4	313	54.7	5.27 (1.78, 15.61)		
	Total (95% CI)		428		411	100	3.54 (1.52, 8.23)		
	Total events	25		7					
	Heterogeneity: $\lambda$ Test for overall e	· ·	•	<i>,</i> ,			0.01 Favors	0.1 1 10 s (experimental) Favors (control)	100
в	Study or subgroup	Experim Events	ental Total	Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl	
в	subgroup	Events	Total			(%)	M–H, fixed, 95% CI		
В	•	•			<b>Total</b> 98 313	-			
В	subgroup Antonia et al <sup>31</sup>	Events 2	<b>Total</b> 115	Events	98	(%) 51.7	M–H, fixed, 95% Cl 1.72 (0.15, 19.22)		
в	<b>subgroup</b> Antonia et al <sup>31</sup> Larkin et al <sup>32</sup>	Events 2	<b>Total</b> 115 313	Events	98 313	(%) 51.7 48.3	M–H, fixed, 95% Cl 1.72 (0.15, 19.22) 3.02 (0.31, 29.19)		
в	subgroup Antonia et al <sup>31</sup> Larkin et al <sup>32</sup> Total (95% Cl)	Events 2 3 $5^{c^2=0.11, df^2}$	Total 115 313 428 =1 ( <i>P</i> =0.7	Events 1 1 2 74); <i>I</i> <sup>2</sup> =0%	98 313	(%) 51.7 48.3	M–H, fixed, 95% Cl 1.72 (0.15, 19.22) 3.02 (0.31, 29.19)	M–H, fixed, 95% Cl	 

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.

Α	Study or	Experim	Iontal	Control		Woight	Odds ratio	Odds ratio	
A	subgroup	Events		Events	Total	(%)	M–H, fixed, 95% Cl	M–H, fixed, 95%	CI
	NSCLC	Lvento	Total	LVCIILO	Total	(70)	M-11, 11Xeu, 3376 Of		
	Borghaei et al <sup>25</sup>	8	287	1	268	6.9	7.66 (0.95, 61.63)		
	Brahmer et al <sup>24</sup>	6	131	0	129	3.3	13.41 (0.75, 240.62)		· · · · · · · · · · · · · · · · · · ·
	Herbst et al <sup>27</sup>	31	682	6	309	54.4	2.40 (0.99, 5.83)		
	Reck et al <sup>28</sup>	9	154	1	150	6.6	9.25 (1.16, 73.92)		
	Subtotal (95% CI)	•	1,254	•	856	71.2	4.06 (1.98, 8.33)		
	Total events	54	-,	8			,,		•
	Heterogeneity: $\chi^2=2$		(P=0.4						
	Test for overall effe								
	Melanoma		,	,					
	Ribas et al <sup>29</sup>	6	357	0	171	4.6	6.34 (0.36, 113.24)		
	Robert et al <sup>6</sup>	3	206	0	205	3.4	7.07 (0.36, 137.72)		
	Weber et al <sup>23</sup>	5	268	0	102	4.9	4.28 (0.23, 78.08)		- ,
	Subtotal (95% CI)	0	831	0	478	12.9	5.75 (1.06, 31.19)		
	Total events	14		0					
	Heterogeneity: $\chi^2 = 0$		(P-0 0						
	Test for overall effe								
		01. 2-2.00	( <i>i</i> =0.0						
	Others	44	000		055	<u> </u>	40.00 (4.40.05.40)		
	Bellmunt et al <sup>30</sup>	11	266	1	255	6.8	10.96 (1.40, 85.49)		
	Ferris et al <sup>22</sup>	5	236	1	111	9.2	2.38 (0.27, 20.63)		
	Subtotal (95% CI)	4.0	502	•	366	15.9	6.01 (1.41, 25.73)		
	Total events	16		2					
	Heterogeneity: $\chi^2 = \chi^2$								
	Test for overall effe	ct: Z=2.42	e (P=0.0	2)					
	Total (95% CI)		2,587		1,700	100	4.59 (2.51, 8.37)		◆
	Total events	84		10					
	Heterogeneity: $\chi^2 = 4$	4.42, df=8	(P=0.8	2); /²=0%					
	Test for overall effe						0.01		10 10
	Test for subgroup d	ifferences	$\chi^2 = 0.3$	81, df=2 (F	<b>P=0.86)</b> ;	I2=0%	F	Favors (experimental) F	avors (control)
в									
	Study or	Exporin	ontal	Control		Woight	Odds ratio	Odds ratio	
ט	Study or subgroup	Experim Events		Control Events	Total		Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H. fixed, 95%	CI
J	subgroup	Experim Events		Control Events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95%	i Cl
J	subgroup NSCLC	Events	Total	Events		(%)	M–H, fixed, 95% Cl		5 CI
J	subgroup NSCLC Borghaei et al <sup>25</sup>	Events 3	Total	Events	268		<b>M–H, fixed, 95% Cl</b> 2.82 (0.29, 27.28)		5 CI
J	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup>	Events 3 0	<b>Total</b> 287 131	Events 1 0	268 129	<b>(%)</b> 15.6	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable		s cı
J	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup>	<b>Events</b> 3 0 14	<b>Total</b> 287 131 682	<b>Events</b> 1 0 2	268 129 309	(%) 15.6 41.2	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24)		5 CI
J	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup>	Events 3 0	<b>Total</b> 287 131 682 154	Events 1 0	268 129	(%) 15.6 41.2 15.1	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97)		
J	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Subtotal (95% CI)	<b>Events</b> 3 0 14 4	<b>Total</b> 287 131 682	<b>Events</b> 1 0 2	268 129 309 150	(%) 15.6 41.2	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24)		
J	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Subtotal (95% CI) Total events	Events           3           0           14           4           21	<b>Total</b> 287 131 682 154 <b>1,254</b>	<b>Events</b> 1 0 2 1 4	268 129 309 150	(%) 15.6 41.2 15.1	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97)		
J	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Subtotal (95% CI)	Stress           3           0           14           4           21           0.05, df=2	<b>Total</b> 287 131 682 154 <b>1,254</b> 2 ( <i>P</i> =0.9	Events 1 0 2 1 4 8); /2=0%	268 129 309 150	(%) 15.6 41.2 15.1	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97)		
5	subgroupNSCLCBorghaei et al25Brahmer et al24Herbst et al27Reck et al28Subtotal (95% CI)Total eventsHeterogeneity: $\chi^2$ =(Test for overall effect	Stress           3           0           14           4           21           0.05, df=2	<b>Total</b> 287 131 682 154 <b>1,254</b> 2 ( <i>P</i> =0.9	Events 1 0 2 1 4 8); /2=0%	268 129 309 150	(%) 15.6 41.2 15.1	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97)		
5	subgroupNSCLCBorghaei et al25Brahmer et al24Herbst et al27Reck et al28Subtotal (95% Cl)Total eventsHeterogeneity: $\chi^2$ =Test for overall effectMelanoma	Second state           3           0           14           4           21           0.05, df=2           ct: Z=2.15	<b>Total</b> 287 131 682 154 <b>1,254</b> ( <i>P</i> =0.9 6 ( <i>P</i> =0.0	Events 1 0 2 1 4 8); <i>I</i> <sup>2</sup> =0% 3)	268 129 309 150 <b>856</b>	(%) 15.6 41.2 15.1 <b>71.9</b>	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97) 3.29 (1.11, 9.75)		5 CI
5	subgroup           NSCLC           Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Subtotal (95% Cl)           Total events           Heterogeneity: $\chi^2$ =(           Test for overall effect           Melanoma           Ribas et al <sup>29</sup>	Stress           3           0           14           4           21           0.05, df=2	<b>Total</b> 287 131 682 154 <b>1,254</b> 2 ( <i>P</i> =0.9 6 ( <i>P</i> =0.0 357	Events 1 0 2 1 4 8); /2=0%	268 129 309 150 <b>856</b> 171	(%) 15.6 41.2 15.1	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97) 3.29 (1.11, 9.75) 2.41 (0.12, 50.52)		5 CI
5	subgroup NSCLC Borghaei et al <sup>25</sup> Brahmer et al <sup>24</sup> Herbst et al <sup>27</sup> Reck et al <sup>28</sup> Subtotal (95% Cl) Total events Heterogeneity: χ <sup>2</sup> =( Test for overall effer Melanoma Ribas et al <sup>29</sup> Robert et al <sup>6</sup>	Events           3           0           14           4           21           0.05, df=2           ct: Z=2.15           2           0	<b>Total</b> 287 131 682 154 <b>1,254</b> 2 ( <i>P</i> =0.9 6 ( <i>P</i> =0.0 357 206	Events 1 0 2 1 4 8); <i>I</i> <sup>2</sup> =0% 3) 0 0	268 129 309 150 <b>856</b> 171 205	(%) 15.6 41.2 15.1 <b>71.9</b>	M–H, fixed, 95% Cl 2.82 (0.29, 27.28) Not estimable 3.22 (0.73, 14.24) 3.97 (0.44, 35.97) 3.29 (1.11, 9.75) 2.41 (0.12, 50.52) Not estimable		5 CI
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0.01 0.1 10 100 1 Test for overall effect: Z=2.90 (P=0.004) Test for subgroup differences:  $\chi^2=0.46$ , df=2 (P=0.79);  $I^2=0\%$ Favors (experimental) Favors (control)

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-I, programmed cell death-I.

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.<sup>15</sup> The anti-PD-1 antibodies pembrolizumab and nivolumab have been shown to have

Heterogeneity: χ<sup>2</sup>=0.98, df=5 (P=0.96); l<sup>2</sup>=0%

beneficial effects in several cancers.<sup>6,22-30</sup> 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

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renal cell carcinoma.<sup>7</sup> 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.<sup>34,35</sup> 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.<sup>36</sup> 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.<sup>37</sup> In rare cases, additional immunosuppressive agents, such as azathioprine or cyclosporine, may be needed.<sup>38</sup> 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<sup>39</sup> 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.

### References

- Momtaz P, Postow MA. Immunologic checkpoints in cancer therapy: focus on the programmed death-1 (PD-1) receptor pathway. *Pharmgenomics Pers Med.* 2014;7:357–365.
- Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. *Nat Med.* 2004;10(9):909–915.
- 3. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010; 363(8):711–723.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011; 364(26):2517–2526.
- Hamid O, Robert C, Daud A, et al. Safety and tumor responses with pembrolizumab (anti-PD-1) in melanoma. *NEngl J Med.* 2013;369(2): 134–144.
- 6. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372(26):2521–2532.
- Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018–2028.
- Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387(10030):1837–1846.
- Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012; 366(26):2455–2465.
- 10. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of cutaneous toxicities in patients with solid tumors treated with immune checkpoint inhibitors: a meta-analysis. *Future Oncol.* 2015;11(17):2471–2484.
- Abdel-Rahman O, ElHalawani H, Fouad M. Risk of elevated transaminases in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Expert Opin Drug Saf.* 2015;14(10):1507–1518.
- 12. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis. *Future Oncol.* 2016;12(3):413–425.
- Abdel-Rahman O, ElHalawani H, Fouad M. Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Immunotherapy*. 2015;7(11):1213–1227.
- Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol.* 2014;15(1):69–77.
- Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26): 2443–2454.
- Gettinger S, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-smallcell lung cancer. *J Clin Oncol.* 2015;33(18):2004–2012.
- Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol.* 2016;2(12):1607–1616.
- Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest.* Epub 2017 May 9.
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- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264–269.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1–12.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–188.
- Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2016; 375(19):1856–1867.
- 23. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2015;16(4):375–384.
- Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med.* 2015;373(2):123–135.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015;373(17):1627–1639.
- Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19): 1803–1813.
- Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016; 387(10027):1540–1550.
- Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016;375(19):1823–1833.
- Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol.* 2015;16(8):908–918.
- Bellmunt J, de Wit R, Vaughn D, et al. Keynote-045: open-label, phase III study of pembrolizumab versus investigator's choice of paclitaxel, docetaxel, or vinflunine for previously treated advanced urothelial cancer. N Engl J Med. 2017;376:1015–1026.
- Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (Check-Mate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016; 17(7):883–895.
- 32. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23–34.
- Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol. 2015;33(17):1974–1982.
- Gangadhar TC, Vonderheide RH. Mitigating the toxic effects of anticancer immunotherapy. *Nat Rev Clin Oncol*. 2014;11(2):91–99.
- Cousin S, Italiano A. Molecular pathways: immune checkpoint antibodies and their toxicities. *Clin Cancer Res.* 2016;22(18):4550–4555.
- Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH. Anti-PD-1-related pneumonitis during cancer immunotherapy. *N Engl J Med.* 2015;373(3):288–290.
- Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev.* 2016;45:7–18.
- Lai YC, Lin PC, Lai JI, et al. Successful treatment of erlotinib-induced acute hepatitis and acute interstitial pneumonitis with high-dose corticosteroid: a case report and literature review. *Int J Clin Pharmacol Ther.* 2011;49(7):461–466.
- Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol.* 2017;35(7):709–717.

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