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Incidence of Programmed Cell Death 1 Inhibitor–Related Pneumonitis in Patients With Advanced Cancer
A Systematic Review and Meta-analysis

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IMPORTANCE Programmed cell death 1 (PD-1) inhibitor–related pneumonitis is a rare but clinically serious and potentially life-threatening adverse event. Little is known about its incidence across different tumor types and treatment regimens.

OBJECTIVE To compare the incidence of PD-1 inhibitor–related pneumonitis among different tumor types and therapeutic regimens.

DATA SOURCES A PubMed search through November 10, 2015, and a review of references from relevant articles. For the PubMed search, the following keywords or corresponding Medical Subject Heading terms were used: *nivolumab*, *pembrolizumab*, and *PD-1 inhibitor*.

STUDY SELECTION Twenty-six original articles of PD-1 inhibitor trial results were identified. Among them, 20 studies of melanoma, non–small cell lung cancer (NSCLC), or renal cell carcinoma (RCC) were eligible for a meta-analysis.

DATA EXTRACTION AND SYNTHESIS The data were extracted by 1 primary reviewer and then independently reviewed by 2 secondary reviewers following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Comparisons of the incidence were based on marginal, exact generalized linear models with generalized estimating equations.

MAIN OUTCOMES AND MEASURES Incidence of all-grade and grade 3 or higher pneumonitis and pneumonitis-related deaths.

RESULTS Twenty studies of single-tumor-type trials of PD-1 inhibitor (12 melanoma studies, 5 NSCLC studies, and 3 RCC studies) (a total of 4496 unique patients) were included in the meta-analysis. The overall incidence of pneumonitis during PD-1 inhibitor monotherapy was 2.7% (95% CI, 1.9%-3.6%) for all-grade and 0.8% (95% CI, 0.4%-1.2%) for grade 3 or higher pneumonitis. The incidence was higher in NSCLC for all-grade (4.1% vs 1.6%; $P = .002$) and grade 3 or higher pneumonitis (1.8% vs 0.2%; $P < .001$) compared with melanoma. The incidence in RCC was higher than in melanoma for all-grade pneumonitis (4.1% vs 1.6%; $P < .001$) but not for grade 3 or higher pneumonitis. Four pneumonitis-related deaths were observed in patients with NSCLC in the monotherapy group. Pneumonitis was more frequent during combination therapy than monotherapy for all-grade (6.6% vs 1.6%; $P < .001$) and grade 3 or higher pneumonitis (1.5% vs 0.2%; $P = .001$) in melanoma, with 1 pneumonitis-related death during combination therapy. Multivariable analyses demonstrated higher odds of pneumonitis in NSCLC for all-grade (odds ratio [OR], 1.43; 95% CI, 1.08-1.89; $P = .005$) and grade 3 or higher pneumonitis (OR, 2.85; 95% CI, 1.60-5.08; $P < .001$) and in RCC for all-grade pneumonitis (OR, 1.59; 95% CI, 1.32-1.92; $P < .001$) compared with melanoma. The combination therapy had significantly higher odds than monotherapy for all-grade (OR, 2.04; 95% CI, 1.69-2.50; $P < .001$) and grade 3 or higher pneumonitis (OR, 2.86; 95% CI, 1.79- 4.35; $P < .001$).

CONCLUSIONS AND RELEVANCE The incidence of PD-1 inhibitor–related pneumonitis was higher in NSCLC and RCC and during combination therapy. These findings contribute to enhance awareness among clinicians and support further investigations to meet the clinical needs.

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Supplemental content

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Programmed cell death 1 (PD-1) inhibitors have marked efficacy in the treatment of advanced cancers.[1-4] Currently, 2 agents, nivolumab and pembrolizumab, have been approved for treatment of advanced melanoma and non-small cell lung cancer (NSCLC), and nivolumab has recently been approved for advanced renal cell carcinomas (RCCs). Combination therapy of nivolumab with a CTLA-4 inhibitor, ipilimumab, has also been approved as a treatment option for melanoma.[5,6] These regulatory approvals have resulted in rapidly expanding access and widespread prescribing of these agents in the clinical setting.

Immune-checkpoint blockade by PD-1 inhibitors is associated with a unique set of toxic effects, which are recognized as immune-related adverse events (IRAEs).[7-10] Multiple organ systems can be affected by IRAEs. Among them, pneumonitis during PD-1 inhibitor therapy has been reported as a relatively uncommon but serious and potentially life-threatening IRAE, resulting in pneumonitis-related deaths in phase 1 trials,[2,11,12] and has been recognized as 1 of the events of special interest.[2,4,13]

Although most clinical trials have reported pneumonitis as an IRAE during PD-1 inhibitor therapy, there has been no report of a systematic review or meta-analysis of the incidence of PD-1 inhibitor–related pneumonitis across different tumor types and between single-agent vs combination therapies. Because this is a relatively rare adverse event, the knowledge based on the individual cohort data from each trial is limited. Given the increasing number of published reports of trial results of PD-1 inhibitors, such an investigation may provide important knowledge of this rare but clinically significant and potentially serious IRAE. We conducted a systematic review and meta-analysis of trials of PD-1 inhibitors in patients with cancer and compared the incidence of pneumonitis among the cohorts with different tumors types and between the groups treated with monotherapy vs combination therapy.

Key Points

Question What is the incidence of programmed cell death 1 (PD-1) inhibitor–related pneumonitis among different tumor types and therapeutic regimens?

Findings In this meta-analysis of 20 published PD-1 inhibitor trials including 4496 patients, the overall incidence of pneumonitis was 2.7% for monotherapy and 6.6% for combination therapy. The incidence was significantly higher in patients with non–small cell lung cancer and renal cell carcinoma than in melanoma and was also higher in the combination therapy group when compared with the monotherapy group.

Meaning Higher incidence of PD-1 inhibitor–related pneumonitis in patients with non–small cell lung cancer and renal cell carcinoma and during combination therapy indicates the need for increased awareness for this clinically significant immune-related adverse event.

Methods

Search Methods and Study Selection

Original articles that have published the results of prospective trials of PD-1 inhibitor therapy for patients with cancer using nivolumab or pembrolizumab, including monotherapy and combination therapy trials, were identified by a PubMed search and by examining the references of published trials, review articles, editorials, and other relevant articles. For the PubMed search, the following keywords or corresponding Medical Subject Heading terms were used: *nivolumab*, *pembrolizumab*, and *PD-1 inhibitor*. The database was searched for articles published on or before November 10, 2015. Articles published online ahead of print were included. Meeting abstracts without published full-text original articles were not eligible for this study. The search focused on the trials of nivolumab and pembrolizumab because these 2 agents have been granted approvals by the US Food and Drug Administration and are widely available by prescription in the clinical setting.

Data Extraction

The total number of patients treated with PD-1 inhibitors, the number of patients with pneumonitis for all grades and for grade 3 or higher, and the number of pneumonitis-related deaths were collected from the eligible articles. Cases listed as pneumonitis were included in the number of pneumonitis events. Other related pulmonary conditions listed separately with the terms *pneumonia* or *interstitial lung disease* were not included. The trial phases, tumor types, types of specific agents (nivolumab or pembrolizumab and additional agents in trials of combination therapy), doses, and frequency of drug administration were recorded. Treatment regimen was classified as PD-1 inhibitor monotherapy or combination therapy. The data extraction was performed by 1 primary reviewer (M.N.) and was then independently reviewed by 2 secondary reviewers (H.H. and N.H.R.) following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Statistical Analysis

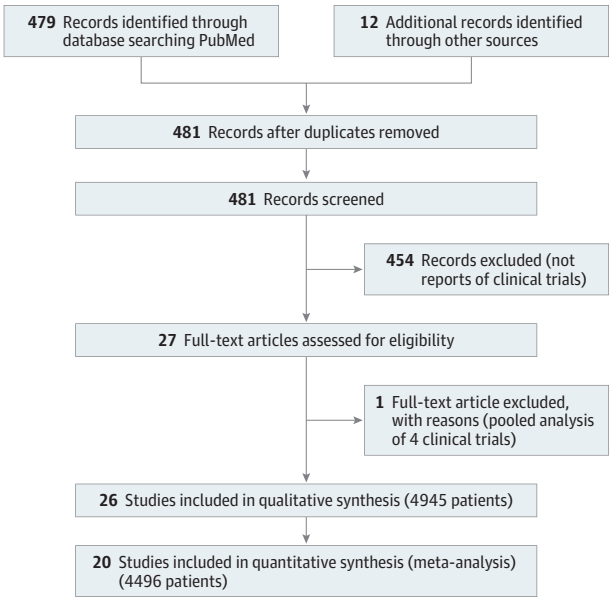
Study Weights

Weights for each study in the analysis were based on the individual sample sizes. In step 1, the percentage of patients contained in each study was calculated based on the total of 4496 patients (ie, 100 × sample size/4496). In step 2, each weight was normalized according to the smallest percentage observed so that the smallest weight was 1. This process was done by dividing the percentage in step 1 by 0.733986, which was the percentage of the total sample for the smallest study. The resulting weights ranged from 1 to 16.8.

Forest Plots

Incidence rates for each study are displayed in forest plots with 95% CIs estimated using exact binomial methods. The overall estimate for each set of graphs was based on the mean weighted incidence from 1000 samples bootstrapped from the subset of studies that met the criteria (eg, monotherapy, monotherapy with lung cancers). The estimated CIs were based on the percentile method, which identified the 2.5% and 97.5% percentile values in the list of 1000 estimated incidence rates from the bootstrap sampling.

Figure 1. Flow Diagram of Study Inclusion



Inference

Comparisons of overall incidence rates between tumor types or monotherapy vs combination therapy were based on marginal, exact generalized linear models. Because the data are correlated by study, estimation used generalized estimating equations.

Multivariable Models

Generalized linear models with generalized estimating equations were fit to assess important predictors of all-grade pneumonitis or grade 3 or higher pneumonitis. Three independent variables were included in each model: tumor type, monotherapy vs combination therapy, and trial phase. Statistical heterogeneity was assessed using Cochrane *Q* statistics,[14] and inconsistency was quantified using I^2 statistics ($100 \times [Q - df]/Q$) that estimate the percentage of total variation across studies attributable to heterogeneity.[15,16] We considered an I^2 value greater than 50% to be indicative of substantial heterogeneity. Publication bias was assessed using Begg and Egger tests with funnel plots.[17,18] For all models, reported *P* values and 95% CIs were adjusted using the Holm-Bonferroni method to preserve overall type I error rates of .05 for each analysis.

Results

Eligible Studies and Characteristics

The PubMed search and the review of reference lists identified a total of 481 records for screening (**Figure 1**). After screening and eligibility assessment, a total of 26 eligible studies (n = 4945 patients) were identified.[1-6,11,12,19-36] Tumor types tested in these studies included melanoma (n = 12), NSCLC (n = 5), advanced solid tumors (n = 4), RCC (n = 3), lymphoma (n = 1), and ovarian cancer (n = 1). These 26 studies were included in a systematic review of the incidence of PD-1 pneumonitis (**Table 1**).

These 26 articles were assessed for inclusion in the meta-analysis, which was primarily designed to compare the incidence of PD-1 pneumonitis among different tumor types. Four studies[1,2,27,28] of advanced solid tumors were removed from the meta-analysis because they included several tumor types, and the breakdown of tumor types of the patients with PD-1 pneumonitis was not always available. In addition, some of these phase 1 studies[2,27] were based on the same multicenter trials that provided the cohorts for the reports that focused on single tumor types and thus may not be completely independent from those in the single-tumor-type studies.[3,4,11,12,23,24] Studies in ovarian cancer[29] and lymphoma[35] were excluded because there is only 1 study for each tumor type with a small sample size. As a result, 20 studies (n = 4496 patients) of single-tumor-type trials (12 melanoma studies,[3-6,19,20,24,26,32-34,37] 5 NSCLC studies,[11,12,21,30,31] and 3 RCC studies[22,23,36]) were included in the meta-analysis.

Three studies[5,6,37] of melanoma reported 2 treatment arms with different regimens (nivolumab monotherapy vs combination therapy[6,37] and concurrent vs sequential therapy for nivolumab and ipilimumab combination[5]). These cohorts were recorded separately, resulting in a total of 29 independent study cohorts from 26 studies for a systematic review and 23 independent study cohorts (15 melanoma, 5 lung, and 3 RCC cohorts) from 20 eligible studies for a meta-analysis.

Incidence of PD-1 Pneumonitis

Table 1 describes the incidence of PD-1 pneumonitis for all-grade and for grade 3 and higher and the incidence of pneumonitis-related death in the 26 studies. The incidence of pneumonitis ranged from 0% to 10.6% for all-grade pneumonitis and from 0% to 4.3% for grade 3 or higher pneumonitis. Pneumonitis-related deaths were reported in 4 studies, with the number of deaths ranging from 1 to 3 (0.2%-2.3%). Of these 26 studies,[1-6,11,12,19-36] 20 studies[3-6,11,12,19-24,26,30-34,36,37] focusing on melanoma, NSCLC, and RCC were assessed in the meta-analysis.

Incidence Among Patients With Melanoma, NSCLC, and RCC Treated With PD-1 Inhibitor Monotherapy

The estimated incidences of pneumonitis based on 1000 bootstrap samples were obtained for patients with melanoma, NSCLC, or RCC treated with monotherapy using single-agent nivolumab or pembrolizumab (eTable in the Supplement). The overall incidence of pneumonitis was 2.7% (95% CI, 1.9%-3.6%) for all-grade pneumonitis (**Figure 2**) and 0.8% (95% CI, 0.4%-1.2%) for grade 3 or higher pneumonitis in the monotherapy group (eFigure 1 in the Supplement).

On the basis of the univariate generalized estimating equation models, including tumor type alone as the predictor, the incidence of pneumonitis in NSCLC was significantly higher compared with melanoma for all-grade pneumonitis (4.1% vs 1.6%; $P = .002$) and grade 3 or higher pneumonitis (1.8% vs 0.2%; $P < .001$). The incidence in RCC was significantly higher compared with melanoma for all-grade pneumonitis (4.1% vs 1.6%; $P < .001$); however, the incidence was not significantly

Table 1. Incidence of PD-1 Inhibitor–Related Pneumonitis in All Studies Included in the Systematic Review

Source	Drug	Tumor Type	Phase	No. (%) of Patients			
				No. of Treated Patients[a]	All-Grade Pneumonitis	Grade ≥3 Pneumonitis	Pneumonitis-Related Death
Brahmer et al,[1] 2010[b]	Nivolumab	Advanced solid tumors	1	39	NA	0	0
Topalian et al,[2] 2012[b]	Nivolumab	Advanced solid tumors	1	296	9 (3.0)	3 (1.0)	3 (1.0)
Hamid et al,[3] 2013	Pembrolizumab	Melanoma	1	135	6 (4.4)	0	0
Wolchok et al,[5] 2013[c]	Nivolumab and ipilimumab (concurrent)	Melanoma	1	53	3 (5.7)	1 (1.9)	0
	Nivolumab and ipilimumab (sequential)	Melanoma	1	33	1 (3.0)	0	0
Weber et al,[37] 2013[c]	Nivolumab	Melanoma	1	41	0	0	0
	Nivolumab and peptide vaccine	Melanoma	1	49	3 (6.1)	2 (4.1)	0
Topalian et al,[4] 2014	Nivolumab	Melanoma	1	107	2 (1.9)	0	0
Robert et al,[24] 2014	Pembrolizumab	Melanoma	1	173	3 (1.7)	1 (0.6)	0
Robert et al,[20] 2015	Nivolumab	Melanoma	3	206	3 (1.5)	0	0
Motzer et al,[22] 2015	Nivolumab	RCC	2	167	8 (4.8)	0	0
Ansell et al,[35] 2015[b]	Nivolumab	Lymphoma	1	23	NA	1 (4.3)	0
Gibney et al,[32] 2015	Nivolumab and peptide vaccine	Melanoma	1	33	1 (3.0)	0	0
Rizvi et al,[21] 2015	Nivolumab	NSCLC	2	117	6 (5.1)	4 (3.4)	0
Weber et al,[19] 2015	Nivolumab	Melanoma	3	268	5 (1.9)	0	0
McDermott et al,[23] 2015	Nivolumab	RCC	1	34	1 (2.9)	0	0
Robert et al,[34] 2015	Pembrolizumab	Melanoma	3	555	6 (1.1)	1 (0.2)	0
Garon et al,[12] 2015	Pembrolizumab	NSCLC	1	495	18 (3.6)	9 (1.8)	1 (0.2)
Postow et al,[33] 2015	Nivolumab and ipilimumab	Melanoma	1	94	10 (10.6)	3 (3.2)	1 (1.1)
Gettinger et al,[11] 2015	Nivolumab	NSCLC	1	129	11 (8.5)	4 (3.1)	3 (2.3)
Patnaik et al,[27] 2015[b]	Pembrolizumab	Advanced solid tumors	1	30	1 (3.3)	0	0
Larkin et al,[6] 2015[c]	Nivolumab	Melanoma	3	313	4 (1.3)	1 (0.3)	0
	Nivolumab and ipilimumab	Melanoma	3	313	20 (6.4)	3 (1.0)	0
Le et al,[28] 2015[b]	Pembrolizumab	Advanced solid tumors[d]	2	41	1 (2.4)	0	0
Brahmer et al,[30] 2015	Nivolumab	NSCLC	3	131	6 (4.6)	0	0
Ribas et al,[26] 2015	Pembrolizumab	Melanoma	2	357	6 (1.7)	2 (0.6)	0
Hamanishi et al,[29] 2015[b]	Nivolumab	Ovarian	2	20	0	0	0
Motzer et al,[36] 2015	Nivolumab	RCC	3	406	16 (3.9)	6 (1.5)	0
Borghaei et al,[31] 2015	Nivolumab	NSCLC	3	287	4 (1.4)	3 (1.0)	0

Abbreviations: NA, not applicable; NSCLC, non–small cell lung cancer; PD-1, programmed cell death 1; RCC, renal cell carcinoma.

[a] Includes the number of patients treated in PD-1 inhibitor arms but does not include patients treated in the control arms without PD-1 inhibitors.

[b] The studies were not included in the meta-analysis.

[c] The studies provided 2 independent cohorts treated with different regimens using PD-1 inhibitors.

[d] Progressive metastatic carcinoma with or without mismatch-repair deficiency.

different for grade 3 or higher pneumonitis. No significant differences were noted between NSCLC and RCC for all-grade pneumonitis or grade 3 or higher pneumonitis. Pneumonitis-related deaths were observed only in patients with NSCLC (4 patients [0.4%]; 95% CI, 0.0%-0.3%) in the monotherapy group.

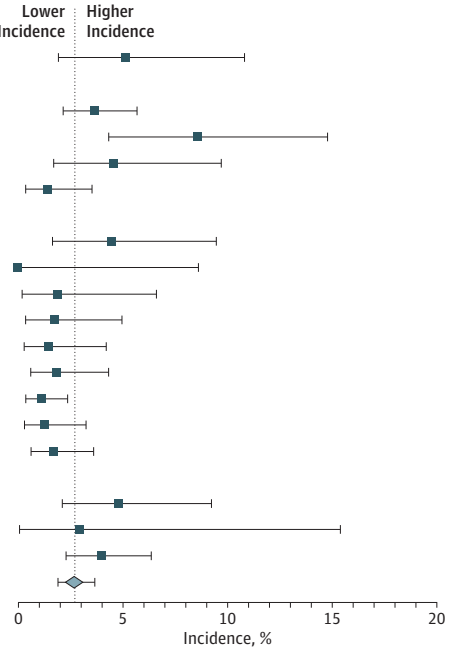
Incidence Between Monotherapy vs Combination Therapy

The incidence of pneumonitis during PD-1 inhibitor monotherapy vs combination therapy was compared in the studies[3-6,19,20,24,26,32-34,37] of melanoma because all studies of combination therapy were conducted in patients with melanoma. Combination regimens included nivolumab and ipili-

Figure 2. Forest Plots of the Incidence of All-Grade Pneumonitis During Monotherapy for Non–Small Cell Lung Cancer (NSCLC), Melanoma, and Renal Cell Carcinoma (RCC)

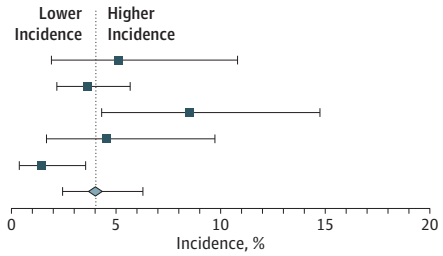
A Incidence of all-grade pneumonitis during PD-1 inhibitor monotherapy in 17 studies in NSCLC, melanoma, and RCC

Source	Incidence, % (95% CI)	Weight
NSCLC		
Rizvi et al,[21] 2015	5.1 (1.9-10.8)	3.5
Garon et al,[12] 2015	3.6 (2.2-5.7)	15.0
Gettinger et al,[11] 2015	8.5 (4.3-14.7)	3.9
Brahmer et al,[30] 2015	4.6 (1.7-9.7)	4.0
Borghaei et al,[31] 2015	1.4 (0.4-3.5)	8.7
Melanoma		
Hamid et al,[3] 2013	4.4 (1.6-9.4)	4.1
Weber et al,[37] 2013	0.0 (0.0-8.6)	1.2
Topalian et al,[4] 2014	1.9 (0.2-6.6)	3.2
Robert et al,[24] 2014	1.7 (0.4-5.0)	5.2
Robert et al,[20] 2015	1.5 (0.3-4.2)	6.2
Weber et al,[19] 2015	1.9 (0.6-4.3)	8.1
Robert et al,[34] 2015	1.1 (0.4-2.3)	16.8
Larkin et al,[6] 2015	1.3 (0.3-3.2)	9.5
Ribas et al,[26] 2015	1.7 (0.6-3.6)	10.8
RCC		
Motzer et al,[22] 2015	4.8 (2.1-9.2)	5.1
McDermott et al,[23] 2015	2.9 (0.1-15.3)	1.0
Motzer et al,[36] 2015	3.9 (2.3-6.3)	12.3
Overall (bootstrap)	2.7 (1.9-3.6)	
Test of heterogeneity: $Q = 31.43$, $P = .01$, $I^2 = 49\%$		



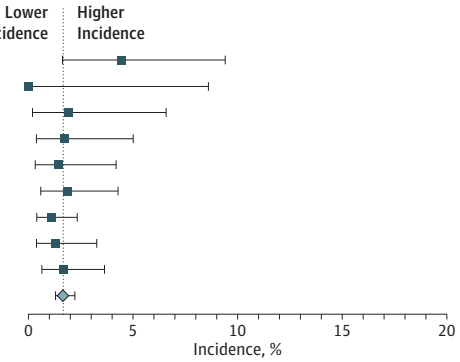
B Incidence of all-grade pneumonitis during PD-1 inhibitor monotherapy in 5 NSCLC studies

Source	Incidence, % (95% CI)	Weight
Rizvi et al,[21] 2015	5.1 (1.9-10.8)	3.5
Garon et al,[12] 2015	3.6 (2.2-5.7)	15.0
Gettinger et al,[11] 2015	8.5 (4.3-14.7)	3.9
Brahmer et al,[30] 2015	4.6 (1.7-9.7)	4.0
Borghaei et al,[31] 2015	1.4 (0.4-3.5)	8.7
Overall (bootstrap)	4.1 (2.4-6.3)	
Test of heterogeneity: $Q = 12.78$, $P = .01$, $I^2 = 69\%$		



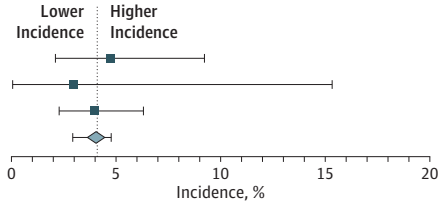
C Incidence of all-grade pneumonitis during PD-1 inhibitor monotherapy in 9 melanoma studies

Source	Incidence, % (95% CI)	Weight
Hamid et al,[3] 2013	4.4 (1.6-9.4)	4.1
Weber et al,[37] 2013	0.0 (0.0-8.6)	1.2
Topalian et al,[4] 2014	1.9 (0.2-6.6)	3.2
Robert et al,[24] 2014	1.7 (0.4-5.0)	5.2
Robert et al,[20] 2015	1.5 (0.3-4.2)	6.2
Weber et al,[19] 2015	1.9 (0.6-4.3)	8.1
Robert et al,[34] 2015	1.1 (0.4-2.3)	16.8
Larkin et al,[6] 2015	1.3 (0.3-3.2)	9.5
Ribas et al,[26] 2015	1.7 (0.6-3.6)	10.8
Overall (bootstrap)	1.6 (1.3-2.2)	
Test of heterogeneity: $Q = 4.20$, $P = .84$, $I^2 = 0\%$		



D Incidence of all-grade pneumonitis during PD-1 inhibitor monotherapy in 3 RCC studies

Source	Incidence, % (95% CI)	Weight
Motzer et al,[22] 2015	4.8 (2.1-9.2)	5.1
McDermott et al,[23] 2015	2.9 (0.1-15.3)	1.0
Motzer et al,[36] 2015	3.9 (2.3-6.3)	12.3
Overall (bootstrap)	4.1 (2.9-4.8)	
Test of heterogeneity: $Q = 0.36$, $P = .84$, $I^2 = 0\%$		

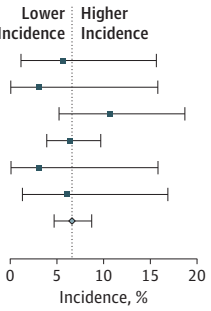


PD-1 indicates programmed cell death 1. Error bars indicate 95% CIs.

Figure 3. Forest Plots of the Incidence of Pneumonitis During PD-1 Inhibitor Combination Therapy in Melanoma

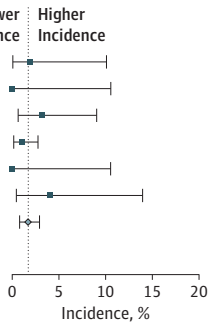
A Incidence of all-grade pneumonitis during PD-1 inhibitor combination therapy in melanoma studies

Source	Incidence, % (95% CI)	Weight
Wolchok et al,[5] 2013[a]	5.7 (1.2-15.7)	1.6
Wolchok et al,[5] 2013[b]	3.0 (0.1-15.8)	1.0
Postow et al,[33] 2015	10.6 (5.2-18.7)	2.8
Larkin et al,[6] 2015	6.4 (3.9-9.7)	9.5
Gibney et al,[32] 2015	3.0 (0.1-15.8)	1.0
Weber et al,[37] 2013	6.1 (1.3-16.9)	1.5
Overall (bootstrap)	6.6 (4.7-8.7)	
Test of heterogeneity: $Q = 4.20$, $P = .52$, $I^2 = 0\%$		



B Incidence of grade 3-5 pneumonitis during PD-1 inhibitor combination therapy in melanoma studies

Source	Incidence, % (95% CI)	Weight
Wolchok et al,[5] 2013[a]	1.9 (0.0-10.1)	1.6
Wolchok et al,[5] 2013[b]	0.0 (0.0-10.6)	1.0
Postow et al,[33] 2015	3.2 (0.7-9.0)	2.8
Larkin et al,[6] 2015	1.0 (0.2-2.8)	9.5
Gibney et al,[32] 2015	0.0 (0.0-10.6)	1.0
Weber et al,[37] 2013	4.1 (0.5-14.0)	1.5
Overall (bootstrap)	1.7 (0.8-2.9)	
Test of heterogeneity: $Q = 2.55$, $P = .77$, $I^2 = 0\%$		



PD-1 indicates programmed cell death 1. Error bars indicate 95% CIs.

[a] The concurrent regimen from the study of nivolumab and ipilimumab by Wolchok et al.[5]

[b] The sequential regimen from the study of nivolumab and ipilimumab by Wolchok et al.[5]

mumab given concurrently or sequentially[5,6,33] and nivolumab plus peptide vaccines.[32,37] One of the combination therapy trials investigated nivolumab plus peptide vaccine as adjuvant therapy for resected stage IIIC and IV melanoma.[32]

The incidence was significantly higher in the combination therapy group compared with the monotherapy group for all-grade (6.6% vs 1.6%; $P < .001$) and grade 3 or higher pneumonitis (1.5% vs 0.2%; $P = .001$) (eTable in the Supplement and **Figure 3**). One pneumonitis-related death was reported in the combination therapy group treated with nivolumab and ipilimumab.

Multivariable Analyses

The results of multivariable analyses are summarized for all-grade pneumonitis and grade 3 or higher pneumonitis (**Table 2**). After adjusting for correlated incidence data and controlling for agents and trial phases, patients with NSCLC were significantly more likely to experience any grade pneumonitis (odds ratio [OR], 1.43; 95% CI, 1.08-1.89; $P = .005$) and grade 3 or higher pneumonitis (OR, 2.85; 95% CI, 1.60-5.08; $P < .001$) compared with patients with melanoma. Patients with RCC were significantly more likely to experience all-grade pneumonitis than patients with melanoma (OR, 1.59; 95% CI, 1.32-1.92; $P < .001$); however, the odds of experiencing grade 3 or higher pneumonitis were not significantly different between the 2 groups (OR, 2.17; 95% CI, 0.68-7.14; $P = .22$). The odds of experiencing pneumonitis were not significantly different between patients with NSCLC and RCC.

After adjusting for correlated incidence data and controlling for tumor types and trial phases, we found no significant differences between nivolumab and pembrolizumab for all-grade pneumonitis and grade 3 or higher pneumonitis. Patients receiving combination therapy were significantly more likely to experience pneumonitis compared with patients receiving monotherapy for all-grade pneumonitis (OR, 2.04; 95% CI, 1.69-2.50; $P < .001$) and grade 3 or higher pneumonitis (OR, 2.86; 95% CI, 1.79-4.35; $P < .001$). When the combination therapy group was subdivided into the nivolumab plus ipilimumab group and the nivolumab plus peptide vaccine group, the nivolumab plus ipilimumab group had significantly higher odds of experiencing pneumonitis than the monotherapy group for all-grade pneumonitis (OR, 2.13; 95% CI, 1.75-2.63; $P < .001$) and grade 3 or higher pneumonitis (OR, 2.78; 95% CI, 1.61-4.76; $P < .001$). The nivolumab plus peptide vaccine group had significantly higher odds of experiencing pneumonitis compared with the monotherapy group for all-grade pneumonitis (OR, 1.54; 95% CI, 1.05-2.27; $P = .03$); however, the difference was not statistically significant for grade 3 or higher pneumonitis (OR, 2.86; 95% CI, 0.83-10.0; $P = .08$). No significant differences were found in the odds of pneumonitis between the nivolumab plus ipilimumab group and the nivolumab plus peptide vaccine group.

After adjusting for correlated incidence data and controlling for tumor and agent, we found that patients in phase 2 trials were significantly more likely to experience pneumonitis compared with patients in phase 3 trials for all-grade pneumonitis (OR, 1.22; 95% CI, 1.06-1.40; $P = .003$); however, no significant differences were observed for grade 3 or higher pneumonitis. Although not statistically significant, a slightly higher likelihood of pneumonitis was also noted in patients in phase 1 trials compared with phase 3 trials for all-grade pneumonitis (OR, 1.30; 95% CI, 0.98-1.71; $P = .07$).

Some study heterogeneity was suggested by the assessment of all-grade pneumonitis in the monotherapy data ($I^2 = 49\%$), which appeared to be concentrated in the studies of NSCLC ($I^2 = 69\%$). There was some evidence of publication bias for all-grade and grade 3 or higher pneumonitis in the monotherapy data (all-grade: Begg test $P = .003$, Egger test $P = .003$; grade ≥3: Begg test $P = .004$, Egger test $P = .001$) but not in the combination data (all-grade: Begg test $P = .83$, Egger test $P = .44$; grade ≥3: Begg test $P = .04$, Egger test $P = .70$). Funnel plots for the monotherapy data are shown to visually demonstrate publication bias (eFigure 2 and eFigure 3 in the Supplement).

Discussion

In the present meta-analysis of the published clinical trial results of PD-1 inhibitor therapy for melanoma, NSCLC, and RCC, the overall incidence of pneumonitis was 2.7% for monotherapy and 6.6% for combination therapy. The incidence was

Table 2. Multivariable Analyses Results for the Incidence of PD-1 Inhibitor–Related Pneumonitis

Variable	All-Grade Pneumonitis		Grade ≥3 Pneumonitis	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Tumor types				
NSCLC (5 studies, 1159 patients) vs melanoma (15 studies, 2730 patients)	1.43 (1.08-1.89)	.005[a]	2.85 (1.60-5.08)	<.001[a]
RCC (3 studies, 607 patients) vs melanoma (15 studies, 2730 patients)	1.59 (1.32-1.92)	<.001[a]	2.17 (0.68-7.14)	.22
NSCLC (5 studies, 1159 patients) vs RCC (3 studies, 607 patients)	0.90 (0.65-1.24)	.42	1.31 (0.43-4.02)	.56
Therapeutic agents				
Nivolumab (12 studies, 2206 patients) vs pembrolizumab (5 studies, 1715 patients)	1.10 (0.86-1.40)	.31	0.71 (0.36-1.42)	.39
Combination therapy (6 studies, 575 patients) vs monotherapy (17 studies, 3921 patients)[b]	2.04 (1.69-2.50)	<.001[a]	2.86 (1.79-4.35)	<.001[a]
Nivolumab and ipilimumab (4 studies, 493 patients) vs monotherapy (17 studies, 3921 patients)	2.13 (1.75-2.63)	<.001[a]	2.78 (1.61-4.76)	<.001[a]
Nivolumab and peptide vaccine (2 studies, 82 patients) vs monotherapy (17 studies, 3921 patients)	1.54 (1.05-2.27)	.03[a]	2.86 (0.83-10.0)	.08
Nivolumab and ipilimumab (4 studies, 493 patients) vs nivolumab and peptide vaccine (2 studies, 82 patients)	1.41 (0.94-2.11)	.07	0.98 (0.30-3.16)	.96
Phase				
Phase 1 (12 studies, 1376 patients) vs phase 2 (3 studies, 641 patients)	1.06 (0.85-1.33)	.51	0.96 (0.40-2.33)	.94
Phase 1 (12 studies, 1376 patients) vs phase 3 (8 studies, 2479 patients)	1.30 (0.98-1.71)	.07	1.29 (0.81-2.06)	.58
Phase 2 (3 studies, 641 patients) vs Phase 3 (8 studies, 2479 patients)	1.22 (1.06-1.40)	.003[a]	1.34 (0.50-3.57)	.94

Abbreviations: NSCLC, non-small-cell lung cancer; PD-1, programmed cell death 1; RCC, renal cell carcinoma.

[a] Statistically significant difference.

[b] Combination therapy includes nivolumab and ipilimumab therapy and nivolumab plus peptide vaccine therapy; monotherapy includes nivolumab and pembrolizumab single-agent therapies.

significantly higher in patients with NSCLC and RCC than in patients with melanoma. Combination therapy was associated with a higher incidence of all-grade and grade 3 or higher pneumonitis compared with monotherapy. Pneumonitis-related deaths were noted in 4 patients with NSCLC in the monotherapy group and in 1 patient with melanoma in the combination therapy group. To our knowledge, this is the first meta-analysis report that focuses on PD-1 inhibitor–related pneumonitis in patients with advanced cancer that compared the incidence among different tumor types and treatment regimens.

A higher incidence of pneumonitis among patients with NSCLC may be because these patients are more prone to develop drug-related lung toxic effects because of their exposure to smoking and underlying lung conditions, including chronic obstructive pulmonary disease and pulmonary fibrosis.[38-40] Existing tumor burden in the lung may also limit the lung tolerance to exogenous stress and injury. A higher incidence among patients with NSCLC for grade 3 or higher pneumonitis may also be explained by similar reasons because these underlying conditions and tumor burden in the lung can contribute to more serious clinical consequences from lung injury during pneumonitis. The incidence for all-grade and grade 3 or higher pneumonitis remained significantly higher for NSCLC compared with melanoma in the multivariable analyses after controlling for agents and trial phases, adding further strength of evidence for this observation. Pneumonitis-related death in the monotherapy group was noted only in patients with NSCLC, again indicating a potentially serious outcome of this adverse event, particularly in NSCLC. These results emphasize a need for increased awareness and careful monitoring of patients with NSCLC during PD-1 inhibitor therapy for the possibility of pneumonitis.

A significantly higher incidence of pneumonitis in patients with RCC compared with patients with melanoma was observed for all-grade pneumonitis but not for grade 3 or higher pneumonitis based on univariate and multivariable analyses. The underlying reasons for these observations remain to be further investigated; however, the results again demonstrate the different susceptibilities of developing PD-1 inhibitor–related pneumonitis among patients with different tumor types and varying effect on their clinical course and outcome.

The incidence of pneumonitis was significantly higher in the combination therapy group compared with the monotherapy group for all-grade and grade 3 or higher pneumonitis among patients with melanoma, indicating the additive effects of 2 agents on lung toxic effects. One death was observed in the melanoma cohort treated with nivolumab and ipilimumab, further indicating the serious consequence of the event during combination therapy. Multivariable analyses, including all 3 tumor types and controlling for tumor types and trial phases, also demonstrated a higher odds of experiencing pneumonitis among the combination therapy group, further supporting the observation. When the combination therapy group was further subdivided into the nivolumab plus ipilimumab group and the nivolumab plus peptide vaccine group, most observations remained significant except that the odds of grade 3 or higher pneumonitis in the nivolumab plus peptide vaccine group were

not significant (OR, 2.86; 95% CI, 0.83-10.0; P = .08). Ipilimumab is another immune-checkpoint inhibitor that acts via the CTLA-4 pathway and is known to be associated with a variety of IRAEs.[9,10,41] Although less clinically apparent and, therefore, less recognized compared with PD-1 inhibitor–related pneumonitis, ipilimumab-associated lung toxic effects have been previously reported in trial and clinical cohorts.[9,42] Although the detailed role and effect of ipilimumab and peptide vaccines on the development and severity of pneumonitis when used in combination with PD-1 inhibitors remain to be further investigated, clinicians should be alerted to the significantly higher incidence of pneumonitis during combination therapy and carefully monitor patients for possible signs and symptoms of pneumonitis.

The incidence of pneumonitis was higher in the phase 2 trials than in the phase 3 trials for all-grade pneumonitis in multivariable analyses. It is possible that the maturation of the trial design based on the knowledge and experiences in earlier-phase trials contribute to lowering the incidence of pneumonitis by optimizing eligibility criteria and monitoring plans.

Limitations of the present study include a relatively small number of eligible studies for meta-analysis; however, all published trial reports of PD-1 inhibitors at the time of data collection have been included to capture the available data in this newly emerging field. Some trials used different doses or frequencies of administration of the therapeutic agents; however, the cohorts were not subdivided according to the dose or frequency because such subdivision will yield more subgroups with smaller sample sizes and because the details of the number of patients with pneumonitis in each subgroup were not consistently available in the published reports. In the data extraction process, the present study only included the number of patients who were specifically listed as experiencing pneumonitis, and other terms, such as *pneumonia* or *interstitial lung disease*, were not included as pneumonitis cases. The approach was chosen to focus on the cases that are clearly noted as pneumonitis and to avoid inclusion of other pulmonary conditions listed under ambiguous terms without detailed description of the specific cases. This meta-analysis focused on the incidence of pneumonitis as a consistently reported variable across different trials; other clinical variables that may be associated with pneumonitis and the incidence of coexisting IRAEs remain to be investigated because these investigations require collection of the individual patient data from multiple trials.

The limitations of using meta-analytic techniques to pool published summary data include concerns about missing studies, heterogeneity of included studies, and the use of aggregated patient data, which can restrict the ability to check for uniform definitions of outcome variables. In the present study, publication bias was present in the monotherapy data, which was particularly concentrated in the NSCLC studies. This finding suggests a need for some caution when interpreting the findings related to these groups because the presence of publication bias may reflect underreporting of small, negative, or nonsignificant studies in the published literature. Further investigations with a larger number of studies in each tumor type and therapeutic regimen may help to validate the observations when more published data become available.

The present study focused on PD-1 inhibitor–related pneumonitis during trials of nivolumab and pembrolizumab and did not include other PD-1 inhibitors or PD-L1 inhibitors because of the paucity of published data at the time of data collection of this study. Likewise, the meta-analysis focused on melanoma, NSCLC, and RCC, and other tumor types, such as lymphoma or ovarian cancer, were not included because of the limited number of published reports with small sample sizes. Three studies[43-45] of the PD-L1 inhibitor atezolizumab have been recently published and have reported the efficacy and safety profiles of the agent in NSCLC, RCC, and urothelial carcinoma. In a phase 2 study of NSCLC, the incidence of atezolizumab-related pneumonitis was 3% (4 of 142 patients) for all-grade and 0.7% (1 of 142) for grade 3 or higher pneumonitis.[43] In a phase 1a study of RCC, the incidence of pneumonitis was 3% (2 of 70 patients) without occurrence of grade 3 or higher pneumonitis.[44] In a phase 2 study of urothelial carcinoma, the incidence was 2% (7 of 310 patients) for all-grade and 1% (2 of 310) for grade 3 or higher pneumonitis.[45] No pneumonitis-related deaths were reported in these studies. Further studies are needed as more data become publicized to compare the incidence of pneumonitis among different agents involved in the PD-1/PD-L1 pathway in a larger variety of tumors. The current study has focused on the 2 PD-1 inhibitors that have been granted the regulatory approvals for the 3 tumor types and have been widely prescribed in the clinical setting to provide the knowledge that is directly relevant to the current clinical practice.

Conclusions

A higher incidence of PD-1 inhibitor–related pneumonitis was noted in patients with NSCLC and RCC and in patients treated with combination therapy. The motives of this meta-analysis were to identify what is known based on the published data and what remains unknown and thus needs to be investigated going forward. In addition to the incidence of pneumonitis across a larger variety of immune-checkpoint inhibitors and tumor types, there remains a significant lack of knowledge of this entity in terms of its risk factors, diagnostic workup strategy, and optimal management guidelines. We strongly believe that systematic investigations of a collection of individual cases of PD-1 inhibitor–related pneumonitis from multiple studies across different institutions will significantly contribute to characterize a full spectrum of clinical and radiographic manifestations of this entity and will serve as the first step to address these remaining clinically urgent questions. It is our sincere hope that the immune-oncology community accelerates its move toward data sharing from multiple studies and promotes multidisciplinary efforts toward the united goal of maximizing the benefits of cancer immunotherapy.

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