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Landscape of Immune-Related Pneumonitis in Cancer Patients with Asthma Being Treated with Immune Checkpoint Blockade

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Abstract

Introduction: Predicting the factors that increase the risk of immune-related pneumonitis, a potentially life-threatening complication of treatment with immune checkpoint inhibitors for cancer, is a clinical challenge. Baseline clinical factors such as asthma may portend the development of pneumonitis due to pre-existing airway inflammation prior to immunotherapy.

Objective: The purpose of the study was to investigate whether a prior diagnosis of asthma is associated with an increased risk of immune-related pneumonitis in patients undergoing cancer immunotherapy.

Methods: Patients at the Moores Cancer Center at UC San Diego Health undergoing immunotherapy were identified on an IRB-approved protocol. Clinical charts were reviewed for asthma documented in the medical records and CT scans were reviewed during and after treatment. Pneumonitis was defined as the onset of new pulmonary symptoms with characteristic imaging findings during or after a patient's first course of immunotherapy that could not be readily explained as infection or a progression of malignancy. It was graded according to the Common Terminology Criteria for Adverse Events.

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Author Contributions

J.G.S. collected, analyzed, and interpreted the patient data and was a major contributor in writing the manuscript. A.T. contributed to data collection and analysis. L.T. participated in data analysis and finalized the tables for the manuscript. A.W. contributed with database setup and research implementation. T.A.D. contributed to editing the final manuscript, in particular with regard to the immune mechanisms of asthma. S.P.P. obtained IRB approval, oversaw the study design, data collection, and analysis, and was the primary editor of the manuscript.

This research project was conducted in accordance with the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent and the study protocol was approved by UC San Diego's committee on human research.

Disclosure Statement

J.G.S., A.T., A.W., and L.T. have no conflicts of interest. T.A.D. declares that he is supported by the NIH/NIAID. S.P.P. declares that he receives scientific advisory income from AstraZeneca, Bristol-Myers Squibb, Illumina, Nektar, and Tempus, and research funding from Bristol-Myers Squibb, Eli Lilly, Incyte, AstraZeneca/MedImmune, Merck, Pfizer, Roche/Genentech, Xcovery, Fate Therapeutics, Genocea, and Iovance.

Results: A total of 187 patients were included. A diagnosis of asthma was found in the records of 26 cases (13.9%). Pneumonitis was found in 10 cases (5.35%); 50% were grade 2 and 50% were grade 3–4. Two of the grade 3–4 cases (40%) occurred in patients with non-small-cell lung cancer. Three patients with asthma developed pneumonitis (11.5% of patients with asthma), all grade 3–4. Only 28.6% of the non-asthma-pneumonitis cases were grade 3–4. All (100%) of the asthma-pneumonitis patients were former smokers, while 71.4% of the non-asthma-pneumonitis patients were former smokers.

Conclusion: A history of asthma may be associated with a higher grade of pneumonitis if it develops, and a history of smoking may augment this relationship.

Keywords

Asthma; Pneumonitis; Immune-related adverse events; Immunotherapy; Checkpoint inhibitors

Introduction

Immune checkpoint inhibitors, including cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death-1-ligand (PD-L1) inhibitors are effective treatments for an increasing number of malignancies, but are associated with immune-related adverse events (irAEs) resulting from off-target T cell-mediated inflammation involving many different organ systems. Pneumonitis, defined as focal or diffuse inflammation of the lung parenchyma, is a rare but potentially life-threatening irAE. Three deaths from immune-related pneumonitis were reported in the early clinical trials with immune checkpoint inhibitors, prompting immediate investigation into the prediction, diagnosis, and treatment of this drug side effect [1].

Immunotherapy-induced pneumonitis is a diagnosis of exclusion in which infection and malignant infiltration must be ruled out. The overlapping respiratory signs and symptoms of cough, shortness of breath, and hypoxemia create a diagnostic challenge. Many cases of pneumonitis are low grade and resolve after stopping the immunotherapy agent and treating with steroids [2, 3]. Pneumonitis is graded according to the Common Terminology Criteria for Adverse Events (CTCAE), with higher grades corresponding to the occurrence of more function-limiting symptoms and the need for more intensive interventions. Any-grade pneumonitis has been shown to develop in approximately 5% of patients treated with anti-PD-1/PD-L1 monoclonal antibodies, with 1–2% developing grade ≥3 disease [4].

An assessment of the risk factors for pneumonitis and other life-threatening irAEs (e.g., colitis, pancreatitis, and hepatitis) is a growing clinical need in the effort to personalize and predict the side effects of cancer therapy. Studies have suggested that the presence of chronic inflammation prior to immunotherapy, e.g., in diseases such as rheumatoid arthritis, lupus, and multiple sclerosis, can confer an increased risk of irAEs that involve the target organ of prior injury (e.g., joints, nervous system, etc.) [5].

Asthma is the most common chronic disease of childhood and affects approximately 8% of the US population (CDC 2016). Asthma is a disease of chronic airway inflammation characterized by the increased presence of eosinophils, lymphocytes, activated mast cells,

Th2 lymphocytes, and group 2 innate lymphoid cells (ILC2s) in the airways and smooth muscle [6]. Chronic activation of these cells may lead to airway remodeling through smooth-muscle hyperplasia and subepithelial fibrosis that can result in decreased lung function over time. While the symptoms in certain childhood asthmatics may improve with age, if asthma is not diagnosed and treated early, the damage to the airways can persist into adulthood.

A prior diagnosis of asthma has not been associated with immune-related pneumonitis. One study investigating pembrolizumab (an anti-PD1 biologic) for the treatment of metastatic non-small cell lung cancer (NSCLC) found that pneumonitis occurred more frequently in patients with a history of asthma and chronic obstructive pulmonary disease (COPD) than in those without this history (5.4 vs. 3.1%) [7]. No other studies have supported this observation and no prospective studies exist examining this question. Additionally, in the above study, asthma and COPD were grouped together, which could be inappropriate given that the pathophysiology and dominant immunologic mechanisms involved differ [8]. Additionally, studies suggest that tobacco use disorder may be an independent risk factor for the development of immune-related pneumonitis, and this may be difficult to distinguish from the risk conferred by a diagnosis of COPD [4].

Given the high prevalence of asthma in the general population and the clinical imperative to determine the comorbidities that might increase a patient's risk of immune-related pneumonitis, we sought to investigate whether a prior diagnosis of asthma was associated with the incidence of immune-related pneumonitis.

Materials and Methods

Patients at the Moores Cancer Center at UC San Diego (La Jolla, CA, USA) for whom immunotherapy treatment was planned were identified. A total of 187 patients were included and their first course of immunotherapy was analyzed.

Each patient's clinical chart was reviewed, and relevant information was collected including cancer type, immunotherapy prescription, duration of therapy, and the development of irAEs. Each chart was reviewed for the presence of asthma listed in the medical record (not necessarily verified with pulmonary function tests and not necessarily undergoing active treatment). For the patients with asthma, we recorded the asthma designation, active medication prescriptions (or medications prescribed at the time of death), emergency department (ED) visits or hospitalizations for asthma exacerbations, and the presence or absence of pulmonary function tests (PFTs). Smoking status was also determined. We excluded patients with COPD, but not those with asthma/COPD overlap. For the patients who developed pulmonary symptoms (cough, shortness of breath, and chest pain) at any point during their immunotherapy treatment, the CT scan imaging was reviewed to determine the presence of pneumonitis.

Pneumonitis was defined as new pulmonary symptoms that developed during the period of immunotherapy accompanied by characteristic CT scan findings including, but not limited to, the 4 major radiologic patterns previously described by Nishino et al. [9, 10], i.e., cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia (NSIP),

hypersensitivity pneumonitis (LIP), and acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS). The standard-of-care radiology report was reviewed by the investigator and first author, and then interpreted along with the clinical context from the medical oncology note.

Infection or progression of malignancy was either excluded or determined to be less likely in the clinical context. Treatment with an anti-inflammatory agent (e.g., steroids) was most often a contributing factor but not required to make the diagnosis. The identification of pneumonitis thus required further chart review to investigate whether an infectious workup should be undertaken, or if this scan was a transition point indicating progression of disease that warranted a change in oncologic therapy.

Pneumonitis was graded according to the CTCAE. Grade 1 pneumonitis is defined as asymptomatic, with clinical or diagnostic observations only, and for which intervention is not indicated. Grade 2 pneumonitis is defined as symptomatic disease, limiting the instrumental activities of daily living, and medical intervention is indicated. Grade 3 pneumonitis is defined as severe symptomatic disease, limiting self-care daily activities, and oxygen administration is indicated. Grade 4 pneumonitis is defined as life-threatening respiratory compromise for which urgent intervention is indicated (e.g., tracheotomy or intubation). Grade 5 pneumonitis is synonymous with death. As the presence of pulmonary symptoms was a requirement in our cohort, we examined only the grade 2–5 pneumonitis cases.

Statistical analyses were performed using MedCalc Online (https://www.medcalc.org/, MedCalc Software, Ostend, Belgium). The odds ratio (OR) and the 95% confidence interval (CI) were calculated according to Altman (1991) [11]. The *p* value was calculated according to Sheskin [12].

Results

Study Population Characteristics

In our cohort of 187 cases, 54.5% were male and 45.5% female (Table 1) with a mean age of 60 years. The major cancer types represented included head and neck (22.5%), lung (18.7%), skin (17.1%), and gastrointestinal (17.1%) cancers. A variety of immunotherapies were used and 46.5% of the therapies were part of clinical trials (Table 2). The most common immunotherapy regimens utilized were anti-PD-1/PD-L1 monotherapy (42.2%), novel anti-PD-1/PD-L1 combination therapy as part of a clinical trial (21.9%), chemotherapy + anti PD-1/PD-L1 combination therapy (11.2%), and anti-CTLA-4 + anti-PD-1/PD-L1 combination therapy (10.2%).

The Relationship of Asthma and Immune-Related Pneumonitis

A diagnosis of asthma was found in the medical record of 26 cases (13.9%; Table 3). Of the patients with asthma in the cohort, 65% were female and 25% were male. The majority had unspecified asthma (46%), followed by asthma/COPD overlap (35%) and childhood asthma (19%). Multiple medication regimens were described. The most common of these was no therapy (28%), followed by short-acting bronchodilator (SABA) monotherapy (21%), and

SABA + long-acting bronchodilator/inhaled corticosteroid dual therapy (4%). On average, the patients did not have any ED visits or hospitalizations specifically for asthma exacerbations in the medical record, though 1 patient averaged approximately 3 exacerbations per year. 30% of patients had undergone pulmonary function tests.

Pneumonitis was found in 10 cases (5.35%); 5 cases were grade 2 (50%), 3 cases were grade 3 (30%), and 2 cases were grade 4 (20%; Table 4). There were 3 patients with a history of asthma who developed pneumonitis, corresponding to 11.5% of the asthma patients compared to 4.34% of the non-asthma patients (Table 5). These 3 patients were all female, 50–60 years of age, and former smokers, compared to 71.4% former smokers among the non-asthma-pneumonitis patients (Table 6). The non-asthma-pneumonitis cases also demonstrated a female predominance (71.4%). Pneumonitis was grade 3–4 in all of the cases of asthma-pneumonitis, but in only 28.6% of the non-asthma-pneumonitis cases. In all cases of pneumonitis, immunotherapy was discontinued. A variety of CT scan findings accompanied the cases of pneumonitis identified. No clear patterns emerged to differentiate the asthma-pneumonitis from the non-asthma-pneumonitis imaging findings. The CT images of the asthma-pneumonitis cases are shown in Figure 1.

Pneumonitis Risk and Cancer Type

Among the 10 cases of pneumonitis, 40% of the events occurred in patients with NSCLC and 20% in patients with head and neck cancer. Of the 5 patients that developed grade 3–4 pneumonitis, 2 cases (40%) occurred in patients with NSCLC (Table 4).

Discussion

Severe and potentially fatal immune-mediated pneumonitis remains one of the most vexing side effects of immune checkpoint blockade therapy, given the broad differential diagnosis and the lack of robust therapies beyond steroids. While the size of our cohort limited the ability to make statistically significant claims about the relationship of asthma to the incidence of pneumonitis, our qualitative comparison of cases of asthma-pneumonitis and non-asthma-pneumonitis was illuminating as real-world evidence from the utilization of immune checkpoint modulators can guide our understanding of irAE risk in patients based on baseline factors. A prospective study would be needed to definitively assess this risk, though logistically challenging.

Our results validate prior findings, specifically that among patients treated with immune checkpoint inhibition, pneumonitis is uncommon, with a prevalence of approximately 5.35% all-grade and 2.67% grade 3–4 pneumonitis, similar to results reported by Naidoo et al. [4] and Nishino et al. [13]. There were no fatalities reported in our study. Our study found an 11.5% incidence of pneumonitis in patients with asthma, although this corresponded to only 3 patients. Due to the small size of our cohort, we cannot draw conclusions about the incidence of pneumonitis in asthma patients versus non-asthma patients. However, the results do suggest that, if pneumonitis does develop, it may be higher grade in asthma-pneumonitis patients, as all 3 of these patients had grade 3–4 pneumonitis.

The important cofounder when comparing asthma-pneumonitis to non-asthma-pneumonitis was a history of smoking. All of the patients with asthma who developed pneumonitis had a history of smoking versus 71.4% in the non-asthma-pneumonitis group, and all of the patients with grade 3–4 pneumonitis were former smokers. Our data therefore suggest that smoking may augment the association between asthma and pneumonitis, or be a strong independent predictor. Smoking has been associated with non-eosinophilic asthma phenotypes, those with low-grade type-2 inflammation [14, 15]. One possible explanation for smokers' increased propensity to develop pneumonitis in the setting of immune checkpoint inhibitors is the exacerbation of pre-existing type-1 inflammation.

It is known that the incidence of pneumonitis is associated with cancer type. Nishino et al. [16] found that the incidence and severity of pneumonitis was higher in NSCLC patients than in those with melanoma and renal cell carcinoma. As well, treatment-naive NSCLC patients have been found to have a higher incidence of all-grade pneumonitis than previously treated patients [17]. Our data also suggest that NSCLC appears to be a strong predictor of the development of pneumonitis, although a history of smoking may the more predictive element. One important limitation of this study was that we were un-able to do a multivariate analysis due to the small sample size.

In the effort to personalize cancer therapy, understanding each patient's unique risk of irAEs is critically important and necessarily depends on clarifying comorbidities, particularly chronic inflammatory diseases of the respiratory tract such as asthma. Current knowledge about the role of PD-L1 in asthma pathogenesis can provide context when trying to understand T cell function and regulation in the asthmatic lung prior to contact with an immune checkpoint inhibitor. PD-1 binds to both PD-L1 and PD-L2. PD-L1 and PD-L2 have been shown to play opposing roles in asthma pathogenesis that relate to airway hyperresponsiveness and T-lymphocyte function in the lung [18]. In mice, PD-L1 deficiency leads to reduced airway inflammation, but PD-L2 deficiency results in increased airway hyperresponsiveness when compared to wild-type mice [13]. The mechanism of this observation depends on a number of different factors including the differential expression of PD-L1 and PD-L2 in lung tissue as well as the cytokine milieu and the downstream effect of these cytokines on different T cell lineages.

PD-L1 is constitutively expressed on dendritic cells, T cells, B cells, and macrophages, but PD-L2 expression is more localized to the lung and has been found to be elevated in dendritic cells from the lung and draining lymph nodes upon challenge [18]. It has been shown that in allergic asthma, the ratio of Th1:Th2 cells is highly skewed toward the Th2 phenotype, promoting airway hyperresponsiveness and mucous production. PD-L1 expression has been shown to inhibit IFN-γ production, but PD-L2 expression inhibits IL-4 production which is implicated in asthma pathogenesis [19-21]. Therefore, blockade of PD-L1 could reduce the relative amount of Th2 cytokines, thereby reducing airway hyperresponsiveness and perhaps contributing to reduced allergic inflammation in the lung. This would suggest that patients with allergic asthma might actually experience fewer asthma exacerbations on PD-1 blockade. However, correlating the potential effect of PD-1/PD-L1 blockade in asthma with the phenomenon of immune-related pneumonitis is not as clear. Another important confounder to consider is that many patients with asthma

take inhaled or oral corticosteroids, which may reduce lung inflammation and thus prevent mild cases of pneumonitis at the beginning.

CD4 T cells predominate in immune-related pneumonitis, with a CD4:CD8 ratio of 2.1:1, and they are also mostly monoclonal, suggesting targeted tumor specificity [22]. In a study involving nivolumab monotherapy for metastatic melanoma, Yamazaki et al. [23] found that pretreatment levels of serum IFN-γ, IL-6, and IL-10 were higher in patients with an objective tumor response than in those with tumor progression. However, it is not known if these cytokines are further increased in patients who develop pneumonitis. An additional avenue of study would be to examine the efficacy of immune checkpoint inhibition in patients with allergic asthma, given that the Th2-skewed lymphocyte enrichment in these patients may create a lower relative ratio of IFN-γ than cytokines such as IL-4, IL-5, and IL-13. About 50% of severe asthmatics have type 2-low asthma. Further research is needed to compare the incidence of pneumonitis in type 2-low asthma patients with the incidence in type 2-high asthma patients.

Additionally, inhaled corticosteroids may counteract the therapeutic potential of immune checkpoint inhibition. The search for biomarkers to predict antitumor responses to immune checkpoint inhibitors is an urgent clinical pursuit, but examining these biomarkers in patients who subsequently developing irAEs, particularly pneumonitis, is equally important.

The limitations of this study include its small sample size, retrospective review design, lack of review by and consensus of multiple radiologists, and heterogeneity of treatment regimens. Using the list of diagnoses documented in the electronic medical record to identify a history of asthma likely led to an overestimation of the presence of asthma in our cohort, as it is often overdiagnosed. Objective data such as PFTs were lacking for most of the patients. As well, the extent to which childhood history of asthma is a relevant comorbidity in adulthood is unclear and likely varies among patients. Prospective studies will need to more adequately determine a history of asthma based on established diagnostic criteria. The heterogeneity of the novel immunotherapeutics used in our cohort, many of which were part of clinical trials, was also a weakness of this study, but it may have more accurately reflected real-world practice. Additionally, comparing the pneumonitis treatment regimens of the asthma-pneumonitis and non-asthma-pneumonitis patients was also a challenge, as the interventions (usually corticosteroids) were often used to address presence of underlying COPD as well. Nevertheless, in all cases, immunotherapy was discontinued.

There is no gold standard diagnostic test for pneumonitis, so the clinical basis for diagnosis is imperfect. Review of CT imaging to confirm a diagnosis of pneumonitis is challenging as pneumonitis can be indistinguishable from infection and progression of malignancy. In the patients with pneumonitis in our cohort, a variety of CT scan patterns were found; we did not find any obvious differences between asthma-pneumonitis and non-asthma-pneumonitis patients.

Radiologic findings of immunotherapy-induced pneumonitis can vary. The most common pattern is COP with consolidative ground-glass opacities in a peripheral or peribronchial distribution [9, 10, 24]. The second-most common pattern is NSIP with ground-glass and

reticular opacities in the peripheral and lower lung fields [9, 10, 25]. The AIP/ARDS pattern is less common, but is more associated with higher grades of pneumonitis, while the HP and NSIP patterns are associated with lower grades [9]. Given this variety of radiologic findings, chart review was undertaken for patients with imaging suggestive of pneumonitis to determine if the clinical scenario was consistent with pneumonitis. As chart review has known limitations, we attempted to reduce inter-rater variability by having the same investigator conduct the chart review and review the imaging for all the cases. Lastly, we limited our review to the CT scans of patients with new or worsening pulmonary symptoms while on immunotherapy. We did not include cases of grade 1 pneumonitis, those without symptoms, but with suggestive imaging findings, as the clinical relevance of such cases is low.

Prior to this study, asthma had not specifically been explored as a risk factor for immune-related pneumonitis. Further investigation with a prospective study is necessary to examine patients with verified asthma and their subsequent risk of developing pneumonitis. Future studies may also address whether the immune checkpoint blockade causes a clinically meaningful change in patients' asthma symptoms. However, the results of this study suggest that a prior diagnosis of asthma may be associated with an increased severity of pneumonitis when it develops.

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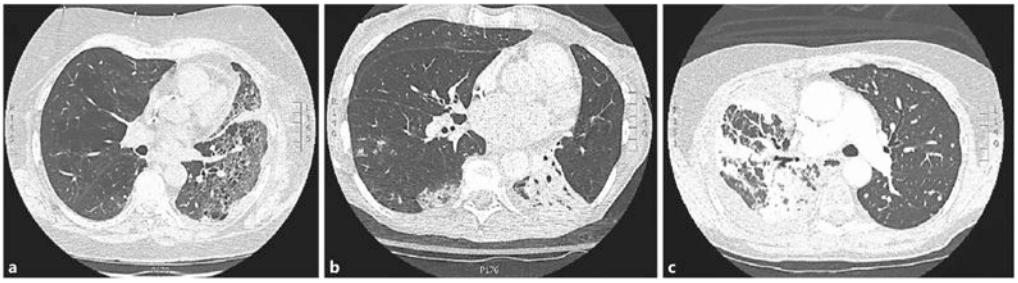

Fig. 1.

a–c Imaging of pneumonitis in 3 patients with asthma showing the first CT scan of the thorax.

Table 1.

Distribution of cancer types in 187 patients treated with immunotherapy

Sex	
Male	102 (54.5)
Female	85 (45.5)
Age, years (mean ± SD)	60±12.6
Type of cancer treated with immunotherapy	
Head and neck	42 (22.5)
Lung	35 (18.7)
Gastrointestinal	32 (17.1)
Skin	32 (17.1)
Breast	13 (7.0)
Gynecologic	10 (5.3)
Endocrine	8 (4.3)
Genitourinary	8 (3.7)
Hematologic	5 (2.7)
Sarcoma	2 (1.1)
Neurologic	1 (0.5)

Values are expressed as *n* (%), unless otherwise indicated.

Table 2.

Distribution of treatment selection in 187 patients undergoing immunotherapy

Anti-PD-1/PD-L1 monotherapy, *n* (%)	79 (42.2)
PD1 inhibitor, *n*	77
Pembrolizumab	49
Nivolumab	28
PDL1 inhibitor, *n*	2
Avelumab	2
Anti-CTLA-4 monotherapy, *n* (%)	5 (2.67)
Ipilimumab, *n*	5
Other monotherapy, *n* (%)	2 (1.07)
Anti-CTLA-4 + anti-PD-1/L-1 combination, *n* (%)	19 (10.2)
PD1 inhibitor + CTLA-4 inhibitor, *n*	17
Pembrolizumab + ipilimumab	1
Nivolumab + ipilimumab	16
PDL1 inhibitor + CTLA-4 inhibitor, *n*	2
Durvalumab + tremelimumab	2
Other combination, *n* (%)	3 (1.60)
Chemotherapy + anti-PD-1/-L1 combination, *n* (%)	21 (11.2)
Novel IO monotherapy, *n* (%)	17 (9.09)
Novel anti-PD-1 plus IO combination, *n* (%)	41 (21.9)

Table 3.

Demographic data of 26 patients with asthma

Mean age, years (SD)	Gender/*n* (%)	Type of asthma/*n* (%)	Prescribed medication/*n* (%)	ED visits or admissions for asthma/*n*	PFT?/ *n* (%)
58 (11)	Male/9 (25)	Unspecified/12 (46)	None/8 (28)	0 per year/20	Yes/8 (30)
	Female/17 (65)	Childhood/5 (19)	SABA only/6 (21)	(77%)	No/18 (70)
		Asthma/COPD overlap/9 (35)	SABA + LABA/ICS/4 (14) SABA + montelukast/2 SABA + ICS/1 SABA + LABA/ICS + montelukast/2 SABA + LABA/ICS + LAMA/1 SABA/SAMA nebs + LABA/ICS + montelukast/1 SABA/SAMA nebs + LABA/ICS + LAMA/1	1 per year/3 2 per year/2 3 per year/1	

Table 4.

Characteristics of 10 patients with pneumonitis

Pneumonitis grade	
Grade 2	5 (50)
Grade 3	3 (30)
Grade 4	2 (20)
Diagnosis of patients with pneumonitis (any grade)	
NSCLC	4 (40)
Head and neck cancer	2 (20)
Melanoma	1 (10)
Uterine cancer	1 (10)
Breast cancer	1 (10)
SCLC	1 (10)
Patients with grade 3–4 pneumonitis	5 (50)
Diagnosis of patients with grade 3–4 pneumonitis	
NSCLC	2 (40)
Head/neck cancer	2 (40)
Melanoma	1 (20)

Values express *n* (%). NSCLC, non-small cell lung cancer

SCLC, small-cell lung cancer.

Table 5.

Asthma and the risk of pneumonitis due to immune checkpoint blockade

	Pneumonitis (any grade)	Without pneumonitis	Total
Asthma	3	23	26 (14%)
Without asthma	7	154	161 (86%)
Total	10 (5.34%)	177 (94.7%)	187

Table 6.

Characteristics of the pneumonitis patients with or without asthma (*n* = 10)

	Malignancy	Immunotherapy	Smoking status	Representative clinical details	Pneumonitis grade
With asthma (*n* = 3)	NSCLC adenocarcinoma (*n* = 2) tongue cancer (*n* = 1)	nivolumab monotherapy (*n* = 1) novel IO combination therapy (*n* = 2)	former smoker (*n* = 3)	(1) Two days after the 1st dose, a 64-year-old female with NSCLC adenocarcinoma and asthma/COPD overlap developed acute hypoxic respiratory failure. She was treated with infliximab and steroid taper. (2) Twenty-five days after the 3rd cycle of IO combination therapy, a 53-year-old female with tongue cancer developed increased shortness of breath and cough, failed outpatient antibiotics, was admitted, and then treated with steroids. There was incomplete resolution of symptoms with the course complicated by recurrent aspiration. (3) Two weeks after the 1st cycle of IO combination therapy, a 54-year-old female with NSCLC adenocarcinoma developed worsening cough and fatigue and was treated with steroids. There was incomplete resolution of symptoms and her course was complicated by a malignant pleural effusion.	Grade 4 (*n* = 2) Grade 3 (*n* = 1)
Without asthma (*n* = 7)	NSCLC adenocarcinoma (*n* = 2) tongue cancer (*n* = 1) melanoma (*n* = 1) uterine cancer (*n* = 1) SCLC (*n* = 1) breast cancer (*n* = 1)	nivolumab monotherapy (*n* = 2) pembrolizumab monotherapy (*n* = 2) pembrolizumab + ipilimumab (*n* = 1) novel IO combination (*n* = 2)	former smoker (*n* = 5) never-smoker (*n* = 2)	(1) One day after day 1 of cycle 13 of pembrolizumab + ipilimumab, a 55-year-old female with triple-negative breast cancer developed acute hypoxic respiratory failure complicated by *Rhinovirus* and *Parainfluenza* pneumonia. She was treated with a prolonged steroid taper. (2) A 78-year-old male with NSCLC adenocarcinoma on pembrolizumab developed fatigue with new ground-glass opacities found on CT scan. He was treated with a steroid taper. (3) On day 28 of the 1st cycle of nivolumab monotherapy, a 64-year-old female with NSCLC presented with worsening shortness of breath. Her course was complicated by pneumonia and worsening heart failure. She was treated with a steroid taper.	Grade 3 (2) Grade 2 (5)