# Risk factors for pneumonitis in advanced extrapulmonary cancer patients treated with immune checkpoint inhibitors

Yasuki Uchida[1*], Daisuke Kinose[1], Yukihiro Nagatani[2], Sachiko Tanaka-Mizuno[3,4], Hiroaki Nakagawa[1], Kentaro Fukunaga[1,5], Masafumi Yamaguchi[1] and Yasutaka Nakano[1]

## Abstract

**Background:** Immune-mediated pneumonitis has a high mortality rate; however, information regarding the related risk factors remains limited. This study aimed to analyze risk factors for pneumonitis, including smoking and lung metastasis (LM), in patients with extrapulmonary primary tumors.

**Methods:** Data of 110 patients treated with immune checkpoint inhibitors (ICIs) (nivolumab/pembrolizumab) for treating extrapulmonary primary tumors at the Shiga University of Medical Science Hospital between January 2015 and December 2019 were retrospectively collected. The association between the onset of pneumonitis and treatment-related factors was analyzed by logistic regression. The severity of pneumonitis was graded according to the Common Terminology Criteria for Adverse Events version 5.0. Risk factors, such as the absence or presence of interstitial lung disease (ILD) and LM, or other clinical factors, including smoking status before ICI administration, were analyzed.

**Results:** Multivariate analyses indicated that the amount of smoking was significantly associated with an increase in the development of all-grade pneumonitis types (odds ratio (OR) = 20.33, 95% confidence interval (CI) = 20.03–20.66; $p = 0.029$). LM and ILD were significantly related to an increase in the development of symptomatic pneumonitis ($\geq$ Grade 2) (OR = 10.08, 95% CI = 1.69–199.81; $p = 0.076$, and OR = 6.76, 95% CI = 1.13–40.63; $p = 0.037$, respectively).

**Conclusions:** Pre-screening for ILD and LM and recognizing patients' smoking history is important for determining the risk of ICI-induced pneumonitis and allowing safe ICI administration.

**Keywords:** Extrapulmonary tumor, Immune checkpoint inhibitors, Lung metastasis, Nivolumab, Pembrolizumab, Pneumonitis

## Background

Immune checkpoint inhibitors (ICIs) are currently the first choice of treatment for several advanced carcinomas [1]. However, with the increasing number of patients receiving ICIs, the incidence of immune-related adverse events (ir-AEs) has also risen. There are various ir-AEs, and their profiles vary depending on the cancer type rather than on the ICI drugs used. AEs in areas located close to the primary lesions tend to occur as ir-AEs. For example, the incidence rate of skin rash during nivolumab (NIVO) therapy is 15% in malignant melanoma, which is higher than that associated with other malignancies, such as non-squamous non-small cell lung cancer (9%), gastric or gastro-esophageal junction cancer (7%), and esophageal squamous cell carcinoma (11%)

*Correspondence: uchiy@belle.shiga-med.ac.jp

[1] Division of Respiratory Medicine, Department of Internal Medicine, Shiga University of Medical Science, Otsu, Japan
Full list of author information is available at the end of the article

Uchida *et al. BMC Cancer* (2022) 22:551

Page 2 of 10

[2–5]. Skin rash incidence during pembrolizumab (PEM) treatment is also higher in melanoma than in other malignancies [6–9]. Diarrhea frequency in association with NIVO is 21% in DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer, while it is 8% in non-squamous non-small cell lung cancer, 16% in melanoma, and 7% in gastric or gastro-esophageal junction cancer [2–4, 10]. Pneumonitis is a potentially serious complication associated with checkpoint inhibitors, defined as focal or diffuse inflammation of the lung parenchyma. Asymptomatic patients can be treated by drug cessation alone or may be acceptable for follow-up, whereas symptomatic patients need the administration of glucocorticoids, including prednisone, with close follow-up and drug cessation. Additional immunosuppression, including infliximab or cyclophosphamide or intravenous immunoglobulin and mycophenolate mofetil, may be needed if the patient's condition worsens, although the benefit from these treatments is unclear. Even after recovery, it is recommended that patients with moderate or severe disease should not resume treatment. Hypoxia may occur and progress rapidly, leading to death [11–13]. As reported based on the univariate generalized estimating equation model for programmed cell death 1 inhibitor-related pneumonitis, non-small cell lung cancer is related to a significantly higher incidence of pneumonitis than melanoma for all-grade pneumonitis (4.1% vs. 1.6%; $p = 0.002$). Comparing the incidence of pneumonitis, non-small cell lung cancer does not show incidence rates significantly different from those of renal cell carcinoma [14]. Both carcinomas have been previously implicated in smoking and carcinogenesis; thus, smoking-related cancers, such as lung cancer and renal cell carcinoma, may be linked to pneumonitis. Patients with lung cancer are more likely to be affected by smoking, and the lesions are located in the lungs; as a result, the frequency of pneumonitis is higher. However, the risk of developing pneumonitis from smoking and lung lesions in patients with other types of cancer, except lung cancer, is unknown. Other than the presence of interstitial lung disease (ILD) [15–18] and differences in carcinoma, the risk factors for pneumonitis are unclear. Therefore, we analyzed risk factors, including smoking and lung metastasis (LM), for pneumonitis in extrapulmonary primary tumors. To determine the risk of pneumonitis, the risk of developing all grades of pneumonitis, including asymptomatic pneumonitis, was examined. We also focused on pneumonitis with symptoms as we suspected this was clinically important. Asymptomatic pneumonitis can only be followed up, whereas symptomatic pneumonitis requires treatment, including steroid administration, and can progress to a more severe condition if left untreated. In this study, identifying risk factors for immune checkpoint inhibitor-induced pneumonitis is expected to help clarify matters that should be checked before administering immune checkpoint inhibitors.

## Methods

### Study design and participants

Data of 110 patients with advanced head and neck cancer, gastric cancer, renal cell cancer, urothelial cancer, peritoneal mesothelioma, and melanoma who were treated with programmed cell death 1 inhibitor (NIVO or PEM) at the Shiga University of Medical Science Hospital between January 2015 and December 2019 were retrospectively collected. To analyze the effect of LM, cancers originating from the lung fields, such as lung cancer, pleural mesothelioma, and primary pulmonary melanoma, were excluded. LM included pleural lesions with or without pleural effusions, but not pleural effusions alone with no histological evidence of disease to exclude pleural effusions of other causes. The number and distribution of pulmonary metastases were not considered, but their presence or absence was assessed. Patients simultaneously treated with other cancer therapies involving cytotoxic agents, except ICIs, were excluded. The patients treated with sequential cytotoxic/targeted therapy were included. All patients received the first ICI regimen, and patients who re-challenged ICI were excluded. This retrospective study was approved by the Institutional Review Board of Shiga University of Medical Science (R2020-037), which waived the need for written informed consent from the patients owing to the retrospective study design.

### Medical record review

The severity of pneumonitis was graded according to the Common Terminology Criteria for Adverse Events version 5.0. The diagnosis of pneumonitis was established, and the evaluation of its severity was performed based on the patients' clinical symptoms, physical examination findings, and radiographic images through a medical record review. The diagnostic criteria for pneumonitis were as follows: (1) new consolidation or ground-glass abnormality on both or any sides on chest computed tomography (CT) during treatment with ICI; (2) exclusion of pulmonary embolism using an electrocardiogram, laboratory data, contrast-enhanced CT, and echocardiography; (3) exclusion of pulmonary infection (i.e., pneumonitis that does not improve even after antibiotic therapy, or when cultures of sputum or bronchoalveolar lavage fluid are free of bacteria); (4) exclusion of heart failure using an electrocardiogram, laboratory data, and echocardiography (asymptomatic patients without CT confirmation were excluded); and (5) exclusion of tumor progression

Uchida *et al. BMC Cancer*     (2022) 22:551

Page 3 of 10

using laboratory data and/or biopsy. In each case of pneumonitis, the pattern of pneumonitis was classified according to the American Thoracic Society/European Respiratory Society statement [19] into (i) organizing pneumonia (OP) pattern, (ii) nonspecific c (NSIP) pattern, (iii) usual interstitial pneumonia pattern, (iv) hypersensitivity pneumonitis pattern, (v) acute interstitial pneumonia/acute respiratory distress syndrome pattern, and (vi) unclassifiable patterns, with reference to preceding studies [20, 21]. All chest CT findings were reviewed by the consensus of a pulmonologist (Yasuki Uchida) and a radiologist (Yukihiro Nagatani). Preexisting ILD was defined using the criteria for ILD of the European Respiratory Society/American Thoracic Society [19]. Other clinical data were collected through a medical record review. The time point for evaluations of smoking status was at the time of ICI initiation. Ever smokers were defined as current and former smokers. Never smokers were defined as those who have never smoked. We evaluated the amount of smoking as pack years.

## Statistical analysis

The characteristics and treatment-related factors of patients with and without pneumonitis or symptomatic and asymptomatic were compared using the Mann–Whitney $U$ test or Fisher's exact test, as appropriate. Odds ratios (ORs) were estimated using logistic regression analysis. All $p$-values were two-sided, and those $\leq 0.05$ were considered statistically significant. Predictors with $p$-values $< 0.10$ in the univariate analysis were included in a multivariate model. ILD is the most common consensus clinical parameter related to the development of pneumonitis [15–18]. We selected ILD from previous studies and also selected the parameters from the results of univariate analysis and performed multivariate analysis. If multiple parameters fulfilled the conditions, the parameter with a $p$-value $< 0.05$ or the smallest $p$-value was included in the multivariate analysis. Moreover, if several smoking-related parameters met the conditions, the amount of smoking was included in the model as it was more specific and related. Two-sided Cohen's κ-coefficients were used to calculate the level of agreement in terms of the pneumonitis pattern in the radiologic assessment between the pulmonologist and the radiologist. All statistical analyses were performed using JMP version 11 (SAS Institute Inc., Cary, NC, USA), R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) [22], and EZR version 1.50 on R commander (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [23].

## Results

### Patient characteristics

The mean duration of pneumonitis onset was 5.6 months, and the mean follow-up period for patients without pneumonitis was 13.3 months. There were 18, 43, 31, 10, 5, 2, and 1 patients with first-line, second-line, third-line, fourth-line, fifth-line, sixth-line, and seventh-line ICI therapy, respectively.

The results of the comparison of the clinical characteristics comparing patients without pneumonitis, asymptomatic (Grade 1) pneumonitis patients and symptomatic ($\geq$ grade 2) patients are shown in Table 1. Comparison between patients with pneumonitis and those without pneumonitis showed significant differences in the amount of smoking ($p = 0.024$) and lung metastasis ($p = 0.029$). Two patients (one with head and neck cancer and the other with urothelial cancer) had received radiotherapy prior to ICI administration, but they did not develop pneumonitis.

Among 110 patients who received ICIs, 19 (17.2%) developed pneumonitis. Table 2 presents clinical details of the 19 patients who developed pneumonitis, and Table 3 shows summaries for 19 people. The OP pattern was most commonly observed (9 out of 19; 47.3%), followed by the NSIP pattern (6 out of 19; 31.6%). Three patients (15.8%) had concomitant NSIP and OP patterns. Hypersensitivity pneumonitis patterns were found in one patient (5.3%). Cohen's κ-coefficient was 0.676.

The median duration between treatment initiation and the occurrence of asymptomatic (G1) and symptomatic ($\geq$ G2) pneumonitis was 3.75 months (range: 0.1–38.1) and 8.0 months (range: 0.2–77.8), respectively.

### Incidence of pneumonitis

Table 4 shows the logistic regression analysis results for the incidence of all-grade and symptomatic pneumonitis. The amount of smoking (OR = 20.35 per 20-pack year increase, 95% CI = 20.06–20.68; $p = 0.018$) and smoking history (ever smoker vs. never smoker [OR = 3.49, 95% CI = 1.06–15.77; $p = 0.038$]) were associated with all-grade pneumonitis. LM (OR = 7.58, 95% CI = 1.39–141.38; $p = 0.015$) and the amount of smoking (OR = 20.39 per 20-pack-year increase, 95% CI = 20.06–20.76; $p = 0.020$) were significantly associated with an increase in the development of symptomatic pneumonitis. In the multivariate analysis, LM was included for symptomatic pneumonitis based on the p-value. The amount of smoking was included for all-grade pneumonitis with ILD. The amount of smoking was included for symptomatic pneumonitis with ILD. Multivariate analyses indicated that the amount of smoking was significantly associated with an increase in the development of all-grade pneumonitis (OR = 20.33, 95% CI = 20.03–20.66; $p = 0.029$), and

Uchida *et al. BMC Cancer*    (2022) 22:551

Page 4 of 10

**Table 1** Patient and treatment characteristics

| Patient characteristics | All patients $n=110$ | No pneumonitis patients $n=91$ | Pneumonitis patients n = 19 | *p*-value No pneumonitis vs pneumonitis (≥ grade 1) |
|---|---|---|---|---|
| Age | | | | 0.44 |
|     Median (range) | 68 (34–84) | 67 (34–84) | 69 (53–81) | |
| Sex | | | | 0.14 |
|     Male | 82 | 65 | 17 | |
|     Female | 28 | 26 | 2 | |
| Smoking history | | | | 0.10 |
|     Current | 25 | 19 | 6 | |
|     Former | 45 | 35 | 10 | |
|     Never | 40 | 37 | 3 | |
| Amount of smoking (pack-years) | | | | 0.024 |
|     Median (range) | 21.75 (0–190) | 15.00 (0–98) | 36.75 (0–190) | |
| Types of cancer | | | | 0.40 |
|     Head and neck cancer | 23 | 17 | 6 | |
|     Gastric cancer | 17 | 14 | 3 | |
|     Renal cell cancer | 29 | 23 | 6 | |
|     Urothelial cancer | 15 | 12 | 3 | |
|     Malignant melanoma | 25 | 24 | 1 | |
|     Peritoneal mesothelioma | 1 | 1 | 0 | |
| BMI (kg/m$^2$) | | | | 0.67 |
|     Median (range) | 20.37 (14.61–36.49) | 20.56 (14.63–36.49) | 20.08 (14.61–32.36) | |
| Immunotherapy | | | | 0.41 |
|     NIVO | 95 | 79 | 16 | |
|     PEM | 15 | 12 | 3 | |
| ILD | | | | 0.068 |
|     Yes | 10 | 6 | 4 | |
|     No | 100 | 85 | 15 | |
| Lung metastasis | | | | 0.31 |
|     Yes | 69 | 55 | 14 | |
|     No | 41 | 36 | 5 | |
| Treatment line | | | | 0.66 |
|     Median (range) | 2 (1–7) | 2 (1–7) | 3 (1–5) | |
| TKI | | | | 1.00 |
|     Yes | 28 | 23 | 5 | |
|     No | 82 | 68 | 14 | |
| CRP (mg/dl) | | | | 0.82 |
|     Median (range) | 0.98 (0.01–11.97) | 0.98 (0.01–11.97) | 0.79 (0.08–10.49) | |
| NLR | | | | 0.33 |
|     Median (range) | 3.84 (0.77–39.78) | 3.79 (1.00–39.78) | 4.46 (0.77–11.36) | |
| **Patient characteristics** | **Asymptomatic (Grade 1) pneumonitis patients** $n=7$ | **Symptomatic (≥ grade 2) pneumonitis patients** $n=12$ | | *p*-value Asymtomatic (≤ grade 1) vs Symptomatic (≥ grade 2) |
| Age | | | | 0.72 |
|     Median (range) | 73 (58–81) | 68.5 (53–74) | | |
| Sex | | | | 0.28 |
|     Male | 6 | 11 | | |
|     Female | 1 | 1 | | |

Uchida *et al. BMC Cancer*      (2022) 22:551

Page 5 of 10

**Table 1** (continued)

| | | | |
|---|---|---|---|
| Smoking history | | | 0.31 |
| Current | 2 | 4 | |
| Former | 4 | 6 | |
| Never | 1 | 2 | |
| Amount of smoking (pack-years) | | | 0.057 |
| Median (range) | 36.00 (0–67.5) | 40.88 (0–190) | |
| Types of cancer | | | 0.090 |
| Head and neck cancer | 4 | 1 | |
| Gastric cancer | 2 | 2 | |
| Renal cell cancer | 0 | 6 | |
| Urothelial cancer | 0 | 3 | |
| Malignant melanoma | 1 | 0 | |
| Peritoneal mesothelioma | 0 | 0 | |
| BMI (kg/m$^2$) | | | 0.69 |
| Median (range) | 20.16 (17.63–25.68) | 20.04 (14.61–32.36) | |
| Immunotherapy | | | 0.21 |
| NIVO | 7 | 9 | |
| PEM | 0 | 3 | |
| ILD | | | 0.077 |
| Yes | 1 | 3 | |
| No | 6 | 9 | |
| Lung metastasis | | | 0.029 |
| Yes | 3 | 11 | |
| No | 4 | 1 | |
| Treatment line | | | 0.073 |
| Median (range) | 2 (1–3) | 2 (3–5) | |
| TKI | | | 0.18 |
| Yes | 0 | 5 | |
| No | 7 | 7 | |
| CRP (mg/dl) | | | 0.71 |
| Median (range) | 0.47 (0.25–10.49) | 1.16 (0.08–9.7) | |
| NLR | | | 0.35 |
| Median (range) | 3.69 (0.77–11.36) | 4.80 (2.35–10.42) | |

*BMI* Body mass index, *NIVO* Nivolumab, *PEM* Pembrolizumab, *ILD* Interstitial lung disease, *LM* Lung metastasis, *TKI* Tyrosine kinase inhibitor, *NLR* Neutrophil-to-lymphocyte ratio

LM was significantly related to an increase in the development of symptomatic pneumonitis (OR = 10.08, 95% CI = 1.69–199.81; $p = 0.076$). In addition, ILD was significantly associated with an increase in the development of symptomatic pneumonitis in the multivariate analysis (6.76, 95% CI = 1.13–40.63; $p = 0.037$).

## Discussion

This study yielded two major findings. First, the amount of smoking was identified as a significant risk factor for the onset of both symptomatic and all-grade pneumonitis. Second, LM was a significant risk factor for developing symptomatic pneumonitis.

For every 20-pack-year increase in the amount of smoking, the risk of symptomatic or all-grade pneumonitis increased by 20.3 times. Current and former smokers had a significantly higher risk of pneumonitis than never smokers. To the best of our knowledge, this study is the first to show that the smoking index is an independent risk factor for ICI-related pneumonitis in extrapulmonary cancer patients. Naidoo et al. showed that the incidence of pneumonitis, including that in lung cancer, was not significantly different between never smokers (19 out of 43 [44%]) and both former/current smokers (24 out of 43 [56%]); however, current smokers showed a tendency toward higher incidence rates than those of former smokers

Uchida *et al. BMC Cancer*     (2022) 22:551

Page 6 of 10

**Table 2** Clinical characteristics of 19 patients with pneumonitis

| Pt | Tumor | sex | Age, year | Agents | ILD | LM | Smoking history | Smoking amount, pack-years | Time to the onset of pneumonitis, day | Grade | Radiographic pattern |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HNC (Sq) | M | 73 | NIVO | − | + | F | 67.5 | 112 | 1 | OP + NSIP |
| 2 | HNC (Sq) | M | 79 | NIVO | + | − | F | 57 | 42 | 1 | OP + NSIP |
| 3 | HNC (Undifferentiated) | M | 68 | NIVO | + | + | F | 48 | 87 | 2 | NSIP |
| 4 | HNC (Sq) | po | 66 | NIVO | − | + | C | 22.5 | 59 | 1 | OP + NSIP |
| 5 | HNC (Sq) | M | 71 | NIVO | − | − | F | 40 | 6 | 1 | OP |
| 6 | HNC (Sq) | M | 69 | NIVO | − | + | C | 50 | 111 | 5 | NSIP |
| 7 | MM | F | 78 | NIVO | − | − | N | 0 | 105 | 1 | OP |
| 8 | GC (AdSq) | M | 72 | NIVO | − | + | C | 26.5 | 456 | 2 | NSIP |
| 9 | GC (Ad) | M | 58 | NIVO | − | + | C | 36 | 20 | 1 | OP |
| 10 | GC (Ad) | M | 81 | NIVO | − | + | F | 15 | 287 | 1 | HP |
| 11 | RCC (clear cell) | M | 74 | NIVO | − | + | F | 36.75 | 771 | 2 | NSIP |
| 12 | RCC (clear cell) | M | 54 | NIVO | − | + | C | 16 | 371 | 2 | OP |
| 13 | RCC (clear cell) | M | 63 | NIVO | − | − | F | 64.5 | 105 | 2 | OP |
| 14 | RCC (clear cell) | F | 64 | NIVO | − | + | N | 0 | 25 | 2 | OP |
| 15 | RCC (clear cell) | M | 73 | NIVO | + | + | F | 22.5 | 129 | 2 | OP |
| 16 | RCC (clear cell) | M | 53 | NIVO | − | + | N | 0 | 1068 | 2 | NSIP |
| 17 | UC | M | 69 | PEM | + | + | C | 12 | 2 | 5 | NSIP |
| 18 | UC | M | 64 | PEM | − | + | F | 102 | 343 | 3 | OP |
| 19 | UC | M | 69 | PEM | − | + | F | 190 | 229 | 2 | OP |

*Ad* Adenocarcinoma, *C* Current, *F* Female, *F* Former, *GC* Gastric cancer, *HNC* Head and neck cancer, *HP* hypersensitivity pneumonitis, *ILD* Interstitial lung disease, *LM* Lung metastasis, *M* male, *MM* Malignant melanoma, *N* Never, *NIVO* Nivolumab, *NSIP* Nonspecific interstitial pneumonia, *OP* Organizing pneumonia, *PEM* Pembrolizumab, *RCC* Renal cell carcinoma, *Sq* Squamous carcinoma, *UC* Urothelial carcinoma

**Table 3** Summary of characteristics of patients with pneumonitis

| Patient characteristics | |
|---|---|
| Age, Median (range) | 69 (53–81) |
| Sex, Male/Female | 17/2 |
| Smoking history Current/Former/Never | 6/10/3 |
| Amount of smoking (pack-years) Median (range) | 36.75 (0–190) |
| Tumor HNC/MM/GC/RCC/UC | 6/1/3/6/3 |
| BMI(kg/m$^2$), Median (range) | 20.08 (14.61–32.326) |
| Immunotherapy, NIVO/PEM | 16/3 |
| ILD, Yes/No | 4/15 |
| LM, Median (range) | 14/5 |
| Treatment line, Median (range) | 3 (1–5) |
| TKI, Yes/No | 5/14 |
| CRP(mg/dl), Median (range) | 0.79 (0.08–10.49) |
| NLR, Median (range) | 4.46 (0.77–11.36) |
| OP/NSIP/OP + NSIP/HP | 9/6/3/1 |

*C* Current, *BMI* Body mass index, *F* Female, *F* former, *GC* Gastric cancer, *HNC* Head and neck cancer, *HP* Hypersensitivity pneumonitis, *ILD* Interstitial lung disease, *LM* Lung metastasis, *M* Male, *MM* Malignant melanoma, *N* Never, *NLR* Neutrophil-to-lymphocyte ratio, *NIVO* Nivolumab, *NSIP* nonspecific interstitial pneumonia, *OP* Organizing pneumonia, *PEM* Pembrolizumab, *RCC* Renal cell carcinoma, *TKI* Tyrosine kinase inhibitor, *UC* Urothelial carcinoma

(5 out of 23 vs. 0 out of 19, $p = 0.053$) [24]. This study did not examine the amount of smoking. Therefore, the results differed slightly from those of our study, but they tend to be consistent with the results of our study. Delaunay et al. reported that most patients who developed pneumonitis were either current (26.7%) or former (53.3%) smokers, with a median consumption of 40 (5–80) pack-years [21]. Our patients had multiple cancer types, although most were non-small cell lung cancers. The smoking index is an independent risk factor for acute exacerbation in patients with cancer complicated by interstitial pneumonia who are receiving cytotoxic anticancer drugs [25]. In terms of other pulmonary diseases, smoking is a risk factor in idiopathic pulmonary fibrosis [26, 27]; however, there is currently a lack of clarity on the involvement of smoking and coexisting emphysema in acute exacerbation events [28–31]. In this study, pre-treatment CT was not taken under the same conditions; thus, the effects of the extent of emphysematous lesions could not be assessed. Concerning radiation pneumonitis, the existing data on smoking and comorbid emphysema as risk factors are inconsistent [32–35]. Conversely, interstitial pneumonia was correlated with symptomatic pneumonitis in this study. Similarly, some studies identified ILD as a

Uchida *et al. BMC Cancer*     (2022) 22:551

Page 7 of 10

**Table 4** Analyses of the incidence of pneumonitis using logistic regression models

| Factor | Symptomatic (≥ G2) pneumonitis | | | | All-grade (≥ G1) pneumonitis | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate Analysis | | Multivariate Analysis | | Univariate Analysis | | Multivariate Analysis | |
| | OR (95% CI) | P-values | HR (95% CI) | P-values | OR (95% CI) | P-values | HR (95% CI) | P-values |
| LM | | 0.015 | | 0.0076 | | 0.26 | | |
| ＋vs － | 7.58 (1.39–141.38) | | 10.08 (1.69–199.81) | | 1.83 (0.64–6.39) | | | |
| Age | | 0.99 | | | | 0.30 | | |
| per 1-year increase | 0.99 (0.95–1.06) | | | | 1.02 (0.98–1.08) | | | |
| Sex | | 0.11 | | | | 0.08 | | |
| Male vs Female | 4.18 (0.76–78.27) | | | | 3.40 (0.89–22.40) | | | |
| Smoking history | | | | | | | | |
| Ever vs Never | 3.03 (0.75–20.44) | 0.13 | | | 3.49 (1.06–15.77) | 0.038 | | |
| Amount of Smoking (pack-years) | | 0.020 | | | | 0.018 | | 0.029 |
| per 20-pack year increase | 20.39 (20.06–20.76) | | | | 20.35 (20.06–20.68) | | 20.33 (20.03–20.66) | |
| BMI (kg/m²) | | 0.90 | | | | 0.99 | | |
| per 1 kg/m² | 1.01 (0.87–1.16) | | | | 1.00 (0.88–1.12) | | | |
| ILD | | 0.071 | | 0.037 | | 0.078 | | 0.12 |
| Yes vs No | 3.78 (0.88–14.90) | | 6.76 (1.13–40.63) | | 4.33 (0.83–18.88) | | 3.19 (0.72–13.01) | |
| Treatment line | | 0.19 | | | | 0.92 | | |
| | 1.36 (0.85–2.12) | | | | 1.02 (0.66–1.51) | | | |
| TKI | | 0.19 | | | | 0.92 | | |
| Yes vs No | 2.33 (0.64–8.01) | | | | 1.06 (0.31–3.11) | | | |
| CRP (mg/dl) | | 0.69 | | | | 0.84 | | |
| | 1.04 (0.84–1.23) | | | | 1.02 (1.18–0.98) | | | |
| NLR | | 0.97 | | | | 0.94 | | |
| | 1.00 (0.83–1.11) | | | | 1.00 (0.88–1.10) | | | |

*OR* Odds ratio, *CRP* C-reactive protein, *CI* Confidence interval, *BMI* Body mass index, *HR* Hazard ratio, *ILD* Interstitial lung disease, *LM* Lung metastasis, *TKI* Tyrosine kinase inhibitor, *NLR* Neutrophil-to-lymphocyte ratio

risk factor for immune-mediated pneumonitis [15–18]. ILD is also a risk factor in radiation pneumonitis [36, 37] and other anticancer drug-related pneumonitis cases [38, 39], which should be noted in pneumonitis. Nishino et al. compared the incidence of pneumonitis in association with PD-1 inhibitor use across different tumor types and reported that the incidence in non-small cell lung cancer was significantly higher in both all-grade (4.1% vs. 1.6%; $p = 0.002$) and ≥ grade 3 (1.8% vs. 0.2%; $p < 0.001$) diseases than in melanoma [14]. If the lesion is located in the chest, such as in lung cancer, the risk of symptomatic pneumonitis may increase. Therefore, symptomatic pneumonitis requires attention regarding the administration of ICIs for cancers that originate outside the chest with pulmonary metastases. To the best of our knowledge, this is the first study to demonstrate a relationship between symptomatic immune-mediated pneumonitis and LM. As the population was limited in this study and the analysis of the relationship between smoking and LM was not the

primary endpoint, it is necessary to validate our findings in a larger number of patients independent of anticancer drug use. Recently, ICI use has been suggested to be associated with the severity of coronavirus disease (COVID-19) and the related rate of hospitalization [40]. Therefore, the presence of viral infection may also need to be examined as a risk factor for pneumonitis. None of the patients in this study had COVID-19, and the disease was still not endemic in Japan at the end of this study.

The diagnosis of drug-induced pneumonitis types, such as immune-mediated pneumonitis, is difficult to establish based on imaging alone and must be considered in conjunction with other examinations, such as clinical history, pulmonary function tests, cardiac evaluation, histopathology, and bronchoscopy. Therefore, the quality of this type of study and patient care would be better if radiologists and respiratory physicians who care for the patient in clinical practice work together. In fact, most of the patients with pneumonitis in this study consulted

Uchida *et al. BMC Cancer* (2022) 22:551

Page 8 of 10

respiratory physicians and were diagnosed through bronchoscopy or other means.

The frequency of pneumonitis varies from 2.7% to 16.9% across reports [14, 16–18, 20, 21, 24, 41]. The incidence of pneumonitis is higher in the Japanese population (13.2–16.9%) [16–18, 41] than in the non-Japanese population (3.5–11.8%) [20, 21, 24]. The Japanese population also tends to have a high incidence of pneumonitis induced using epidermal growth factor receptor tyrosine kinase inhibitors [38, 42]. It is unclear whether this can be attributed to race or the presence of confounding factors unique to Japan, such as the prevalence of interstitial pneumonia or the amount of smoking. Alternately, the fact that there is a tendency to repeat imaging studies in Japan may have facilitated the detection of grade 1 asymptomatic pneumonitis. If the prevalence of pneumonitis is high in the Japanese population and low in the non-Japanese population, it may be easier to investigate risk factors for pneumonitis in Japanese people who are more likely to experience a higher rate of events. It should also be considered that the incidence varies with the follow-up duration.

This study had some limitations. First, it had a retrospective design and included a relatively small number of patients with immune-mediated pneumonitis treated in a single institution. This could be a possible reason for the wide 95% CIs for several factors. The association with grade 3 or higher pneumonitis was too small to analyze. Second, data on asymptomatic pneumonitis during the follow-up of patients with cancers with extrapulmonary origins might have been missed owing to a lack of routine chest imaging evaluations, such as chest radiography. Third, sequential therapy may have influenced the results; however, none of the patients had received EGFR inhibitors. Finally, several performance statuses and pulmonary function parameter values were missing and could not be analyzed. Therefore, validation in a multicenter, prospective study that considers these points is necessary.

## Conclusions

In this study, which aimed to examine the predictors of pneumonitis development risk in association with the administration of ICIs for extrapulmonary tumors, the smoking index was found to increase the risk of pneumonitis regardless of the past or current smoking status. Similarly, interstitial pneumonitis and LM also increased the risk of symptomatic pneumonitis development. Pre-screening for ILD and LM and recording patients' smoking history can aid in the determination of the risk of pneumonitis and ensure safe ICI administration. It is our sincere hope that our findings can be used for the successful management of immune-mediated pneumonitis to increase the life expectancy of cancer patients.

## Declarations

### Ethics approval and consent to participate
This retrospective study was approved by the ethics committee of Shiga University of Medical Science with R2020-037, which waived the need for written informed consent from the patients owing to the retrospective study design. All methods were carried out in accordance with the declaration of Helsinki.

### Consent for publication
Not applicable.

### Competing interests
YU reports lecture fees from Ono Pharmaceutical, MSD, AstraZeneca, Chugai Pharma, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Eli Lilly, and Kyowa Hakko Kirin. DK reports lecture fees from AstraZeneca. YN reports lecture fees from Daiichi-Sankyo and Nippon Shinyaku. STM is an endowed chair from Kyowa Kirin and Eisai. HN reports lecture fees from Nippon Boehringer Ingelheim, Nippon Shinyaku, and AstraZeneca. KF reports lecture fees from Nippon Boehringer Ingelheim, Ono Pharmaceutical, Chugai Pharma, and AstraZeneca. MY reports lecture fees from AstraZeneca, Chugai Pharma, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, GlaxoSmithKline, Boston Scientific, Nippon Shinyaku, KYORIN Pharmaceutical, Novartis Pharma, TEIJIN, Sanofi, Ono Pharmaceutical, Bristol Myers Squibb, Astellas Pharma, MSD, Takeda Pharmaceutical, and Air Water Medical. YN reports lecture fees from AstraZeneca, Chugai Pharma, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, KYORIN Pharmaceutical, Novartis Pharma, Pfizer, Meiji Seika Kaisha, Nippon Kayaku, TEIJIN, and Otsuka Pharmaceutical, and advisor fee from Olympus. No other disclosures were reported.

### Author details
[1]Division of Respiratory Medicine, Department of Internal Medicine, Shiga University of Medical Science, Otsu, Japan. [2]Department of Radiology, Shiga University of Medical Science, Otsu, Japan. [3]Department of Digital Health and Epidemiology, Kyoto University, Kyoto, Japan. [4]The Center for Data Science Education and Research, Shiga University, Hikone, Japan. [5]Department of Respiratory Medicine, Kohka Public Hospital, Kohka, Japan.

Uchida *et al. BMC Cancer*     (2022) 22:551

Page 9 of 10

## References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–23. https://doi.org/10.1056/NEJMoa1003466.
2. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30. https://doi.org/10.1056/NEJMoa1412082.
3. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373:1627–39. https://doi.org/10.1056/NEJMoa1507643.
4. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:2461–71. https://doi.org/10.1016/S0140-6736(17)31827-5.
5. Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:1506–17. https://doi.org/10.1016/S1470-2045(19)30626-6.
6. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med. 2018;378:1789–801. https://doi.org/10.1056/NEJMoa1802357.
7. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375:1823–33. https://doi.org/10.1056/NEJMoa1606774.
8. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376:1015–26. https://doi.org/10.1056/NEJMoa1613683.
9. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, Jr, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394:1915–28. https://doi.org/10.1016/S0140-6736(19)32591-7.
10. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz HJ, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol. 2017;18:1182–91. https://doi.org/10.1016/S1470-2045(17)30422-9.
11. Chuzi S, Tavora F, Cruz M, Costa R, Chae YK, Carneiro BA, et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. Cancer Manag Res. 2017;9:207–13. https://doi.org/10.2147/CMAR.S136818.
12. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2016;2:1346–53. https://doi.org/10.1001/jamaoncol.2016.1051.
13. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36:1714–68. https://doi.org/10.1200/JCO.2017.77.6385.
14. 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;2:1607–16. https://doi.org/10.1001/jamaoncol.2016.2453.
15. Shimoji K, Masuda T, Yamaguchi K, Sakamoto S, Horimasu Y, Nakashima T, et al. Association of preexisting interstitial lung abnormalities with immune checkpoint inhibitor–induced interstitial lung disease among patients with nonlung cancers. JAMA Netw Open. 2020;3: e2022906. https://doi.org/10.1001/jamanetworkopen.2020.22906.
16. Kanai O, Kim YH, Demura Y, Kanai M, Ito T, Fujita K, et al. Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease. Thorac Cancer. 2018;9:847–55. https://doi.org/10.1111/1759-7714.12759.
17. Nishiyama N, Honda T, Sema M, Kawahara T, Jin Y, Natsume I, et al. The utility of ground-glass attenuation score for anticancer treatment-related acute exacerbation of interstitial lung disease among lung cancer patients with interstitial lung disease. Int J Clin Oncol. 2020;25:282–91. https://doi.org/10.1007/s10147-019-01576-x.
18. Nakanishi Y, Masuda T, Yamaguchi K, Sakamoto S, Horimasu Y, Nakashima T, et al. Pre-existing interstitial lung abnormalities are risk factors for immune checkpoint inhibitor-induced interstitial lung disease in non-small cell lung cancer. Respir Investig. 2019;57:451–9. https://doi.org/10.1016/j.resinv.2019.05.002.
19. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48. https://doi.org/10.1164/rccm.201308-1483ST.
20. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. Clin Cancer Res. 2016;22:6051–60. https://doi.org/10.1158/1078-0432.CCR-16-1320.
21. Delaunay M, Cadranel J, Lusque A, Meyer N, Gounant V, Moro-Sibilot D, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J. 2017;50. doi:https://doi.org/10.1183/13993003.00050-2017.
22. Ihaka R, Gentleman R. R: a language for data analysis and graphics. J Comput Graph Stat. 1996;5:299–314. https://doi.org/10.1080/10618600.1996.10474713.
23. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8. https://doi.org/10.1038/bmt.2012.244.
24. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35:709–17. https://doi.org/10.1200/JCO.2016.68.2005.
25. Isobe K, Hata Y, Sakamoto S, Takai Y, Shibuya K, Homma S. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. Respirology. 2010;15:88–92. https://doi.org/10.1111/j.1440-1843.2009.01666.x.
26. Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. Lancet. 1996;347:284–9. https://doi.org/10.1016/s0140-6736(96)90465-1.
27. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1997;155:242–8. https://doi.org/10.1164/ajrccm.155.1.9001319.
28. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J. 2012;40:101–9. https://doi.org/10.1183/09031936.00106011.
29. Collard HR, Richeldi L, Kim DS, Taniguchi H, Tschoepe I, Luisetti M, et al. Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. Eur Respir J. 2017;49. doi:https://doi.org/10.1183/13993003.01339-2016.
30. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356–63. https://doi.org/10.1183/09031936.00159709.
31. Putman RK, Gudmundsson G, Axelsson GT, Hida T, Honda O, Araki T, et al. Imaging patterns are associated with interstitial lung abnormality progression and mortality. Am J Respir Crit Care Med. 2019;200:175–83. https://doi.org/10.1164/rccm.201809-1652OC.
32. Takeda A, Kunieda E, Ohashi T, Aoki Y, Oku Y, Enomoto T, et al. Severe COPD is correlated with mild radiation pneumonitis following stereotactic body radiotherapy. Chest. 2012;141:858–66. https://doi.org/10.1378/chest.11-1193.
33. Uchida Y, Tsugawa T, Tanaka-Mizuno S, Noma K, Aoki K, Shigemori W, et al. Exclusion of emphysematous lung from dose-volume estimates of risk improves prediction of radiation pneumonitis. Radiat Oncol. 2017;12:160. https://doi.org/10.1186/s13014-017-0891-z.
34. Baker R, Han G, Sarangkasiri S, DeMarco M, Turke C, Stevens CW, et al. Clinical and dosimetric predictors of radiation pneumonitis in a large series of patients treated with stereotactic body radiation therapy to

Uchida *et al. BMC Cancer*    (2022) 22:551

Page 10 of 10

the lung. Int J Radiat Oncol Biol Phys. 2013;85:190–5. https://doi.org/10.1016/j.ijrobp.2012.03.041.

35. Tucker SL, Xu T, Paganetti H, Deist T, Verma V, Choi N, et al. Validation of effective dose as a better predictor of radiation pneumonitis risk than mean lung dose: secondary analysis of a randomized trial. Int J Radiat Oncol Biol Phys. 2019;103:403–10. https://doi.org/10.1016/j.ijrobp.2018.09.029.

36. Glick D, Lyen S, Kandel S, Shapera S, Le LW, Lindsay P, et al. Impact of pre-treatment interstitial lung disease on radiation pneumonitis and survival in patients treated with lung stereotactic body radiation therapy (SBRT). Clin Lung Cancer. 2018;19:e219–26. https://doi.org/10.1016/j.cllc.2017.06.021.

37. Ueki N, Matsuo Y, Togashi Y, Kubo T, Shibuya K, Iizuka Y, et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. J Thorac Oncol. 2015;10:116–25. https://doi.org/10.1097/JTO.0000000000000359.

38. Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. Am J Respir Crit Care Med. 2008;177:1348–57. https://doi.org/10.1164/rccm.200710-1501OC.

39. Naito Y, Tsuchiya S, Ishihara S, Minato K, Shitara Y, Takise A, et al. Impact of preexisting pulmonary fibrosis detected on chest radiograph and CT on the development of gefitinib-related interstitial lung disease. Am J Clin Oncol. 2008;31:340–4. https://doi.org/10.1097/COC.0b013e318162f13b.

40. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020;26:1218–23. https://doi.org/10.1038/s41591-020-0979-0.

41. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. Lung Cancer. 2018;115:71–4. https://doi.org/10.1016/j.lungcan.2017.11.019.

42. Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. Lung Cancer. 2015;88:74–9. https://doi.org/10.1016/j.lungcan.2015.01.026.

## Publisher's Note