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Treatment and relapse of interstitial lung disease in nivolumab-treated patients with non–small cell lung cancer

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Abstract

Nivolumab, a human monoclonal antibody against programmed death-1, is approved for the treatment of non–small cell lung cancer (NSCLC). Although nivolumab is generally well tolerated, it can cause interstitial lung disease (ILD), a rare but potentially fatal immune-related adverse event. Currently, there are limited data available on the treatment of nivolumab-induced ILD and its outcome. This retrospective cohort study based on a post–marketing study described the treatment of nivolumab-induced ILD and its outcome in NSCLC patients in Japan through the assessment of clinical and chest imaging findings by an expert central review committee. Treatment details for patients who experienced a relapse of ILD were also analyzed. Of the 238 patients

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Abbreviations: AE, adverse event; CEP, chronic eosinophilic pneumonia; Cont., continued; COP, cryptogenic organizing pneumonia; DAD, diffuse alveolar damage; Disc., discontinued; ECRC, expert central review committee; F, female; Faint infil./HP, faint infiltration/hypersensitivity pneumonia; ILD, interstitial lung disease; M, male; NIV, nivolumab; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; Resp., respiratory; Restart, restarted.

identified as having nivolumab-induced ILD, 37 patients died of ILD. Corticosteroids were used in 207 (87.0%) patients. Of those, 172 (83.1%) patients responded well and survived and 35 (16.9%) died (most died during corticosteroid treatment). A total of nine patients experienced a relapse; at the time of relapse, four patients were taking nivolumab. Of those who were receiving corticosteroids at the time of relapse, three of four patients were taking low doses or had nearly completed dose tapering. All patients (except one, whose treatment was unknown) received corticosteroids for the treatment of relapse, but one patient died. Patients with NSCLC who experience nivolumab-induced ILD are treated effectively with corticosteroids, and providing extra care when ceasing or reducing the corticosteroid dose may prevent relapse of ILD.

KEYWORDS
Adverse drug events, Immunotherapy, Interstitial lung disease, Nivolumab, Non-small-cell lung carcinoma

1 | INTRODUCTION

Nivolumab is a human monoclonal antibody that selectively targets programmed death-1 (PD-1), a surface membrane receptor expressed on activated T cells.[1] When PD-1 is bound by tumor-expressed programmed death ligand-1 (PD-L1) or programmed death ligand-2 (PD-L2), downregulation of T cell activation occurs and the antitumor activity of T cells is inhibited.[2] Through the blockade of PD-1, nivolumab inhibits the interaction between PD-1 and PD-L1/PD-L2 and enhances immune recognition and stimulation of T cells to attack tumor cells.[3] In Japan, nivolumab is approved for the treatment of different types of cancer, including non–small cell lung cancer (NSCLC).[1,4] Nivolumab is generally well tolerated in NSCLC; in two phase III trials, Checkmate 017 and Checkmate 057, adverse events (AEs) were less common and of lower grade with nivolumab than with docetaxel.[2,5]

Owing to their mechanism of action, checkpoint inhibitors such as nivolumab can cause immune-related AEs, including interstitial lung disease (ILD).[1] In the Checkmate 017 and Checkmate 057 trials, nivolumab-induced ILD or pneumonitis was reported in 4.6% (6/131) and 3.5% (10/287) of patients, respectively.[2,5] In ILD, patients may present with severe breathlessness following diffuse alveolar damage, which can be fatal in some patients.[6] As there is currently no specific treatment for ILD, systemic steroids are used and treatment is based on drug-related interstitial pneumonitis treatment.[7] Therefore, information on the treatment of nivolumab-induced ILD will enable the appropriate use of nivolumab in treating different cancers. However, no previous studies have presented detailed data on the treatment of nivolumab-induced ILD in clinical practice settings. In addition, little is known about relapse cases of nivolumab-induced ILD, particularly when nivolumab is continued or restarted following recovery from the initial ILD.

This study was part of a post–marketing study of patients with NSCLC in Japan treated with nivolumab. A previous part of the post–marketing study evaluated radiographic characteristics and poor prognostic factors of ILD and found that a diffuse alveolar damage (DAD)-like radiographic pattern, onset of ILD ≤60 days from nivolumab initiation, pleural effusion before nivolumab treatment, lesion distribution contralateral or bilateral to the tumor, and abnormal changes in C-reactive protein levels were indicative of a poor prognosis.[8] These results may help physicians observe the clinical course of nivolumab-induced ILD more carefully and provide improved care, especially to patients with poor prognostic factors. The aim of the current study was to describe the treatment of ILD in nivolumab-treated patients with NSCLC in Japan, which will provide further information on the management of nivolumab-induced ILD. Furthermore, we present detailed data for patients who experienced a relapse of ILD to investigate whether there are any characteristics that may lead to a relapse after initial resolution.

2 | PATIENTS AND METHODS

2.1 | Study design

This was a retrospective cohort study based on a post–marketing study of patients with NSCLC treated with nivolumab in Japan. Further details are described in a separate report.[8]

2.2 | Study population

Male and female patients of any age with NSCLC who experienced ILD during nivolumab treatment and had clinical findings and chest radiographic images available were included in this study. The clinical data and radiographic images (computed tomography/X-rays) for each nivolumab-treated patient were assessed by the treating physician. Clinical data of patients who were reported as having a drug-induced lung injury were then assessed by an ILD expert central

review committee (ECRC) to determine whether patients were experiencing nivolumab-induced ILD and were eligible for the analysis. The ECRC consisted of eight pulmonologists and eight radiologists; two radiologists independently evaluated the radiographs and two pulmonologists independently evaluated the clinical data. Patients were diagnosed with nivolumab-associated ILD by the ECRC if they had a newly appeared abnormal chest shadow on the radiographic images and if the reported lung disease was considered not to be an infection, heart failure, and/or disease progression. Patients were considered not to have nivolumab-associated ILD and were excluded from the analysis if the clinical data were not evaluable or if another drug could not be ruled out as the cause of ILD. Patients who experienced another ILD following recovery from the initial ILD were identified by the ECRC using the radiographic images and clinical findings and were considered as having an ILD relapse. Relapses in these patients were assessed by the ECRC in the same manner as the initial ILD.

2.3 | Data collection and evaluation

Data collected for patients who were considered by the ECRC to have nivolumab-associated ILD were as follows: the ILD radiographic pattern; treatment details of ILD (drug, dose, and duration of treatment); and treatment outcome (recovered, recovering, not recovered, exacerbation, death, and unknown). If corticosteroids were used, the doses were reported as prednisolone equivalent doses. For patients who experienced ILD relapse, patient baseline demographic characteristics were collected, including age, sex, body weight, disease status of ILD, and radiographic image pattern at the time of relapse. Data were also collected regarding patients' nivolumab treatment status; ie, whether nivolumab was continued or discontinued at initial development of ILD and, if it was discontinued, whether it was restarted between resolution of initial ILD and relapse (and whether patients were taking nivolumab or not at time of relapse). In addition, data were collected on corticosteroid dose (prednisolone equivalent) and duration of treatment, time between resolution of initial ILD and relapse, and treatment outcome of ILD relapse. Collected data were analyzed using descriptive statistics.

3 | RESULTS

3.1 | Patient disposition

Of the 325 nivolumab-treated patients with NSCLC who reported symptoms of ILD between 17 December 2015 and 31 March 2016, 273 patients were identified by the ECRC as having ILD (Figure 1). Of the 273 patients with ILD, nivolumab was determined to be the cause of ILD in 238 patients. In the remaining 35 patients, the effects of other agents could not be excluded, and, therefore, those patients were not included in this evaluation. Of the 238 patients who were included in this study, 37 patients died of ILD.

3.2 | Treatment of initial interstitial lung disease

Corticosteroids were used as the treatment for ILD in 207 patients (87.0%; Table 1). Five patients (2.1%) received immunosuppressants other than steroids; all these patients also received corticosteroids, although not always concurrently. Patients who survived were treated with corticosteroids for a longer duration than patients who died of ILD (Table 2; Figure 2). Many of the deaths from ILD occurred shortly after the onset of ILD; of the 37 patients who died of ILD, the median time between development of ILD and death was 23 days (range, 2-197 days). Discontinuation of corticosteroid treatment and death occurred at almost the same time (Figure 2). Starting doses of corticosteroids administered to patients varied from <0.5 to ≥2.0 mg/kg/day (prednisolone equivalent); 87 patients received corticosteroid pulse therapy. Of the 35 patients who received corticosteroid treatment but died of ILD, 20 patients (57.1%) received corticosteroid pulse therapy (Table 3).

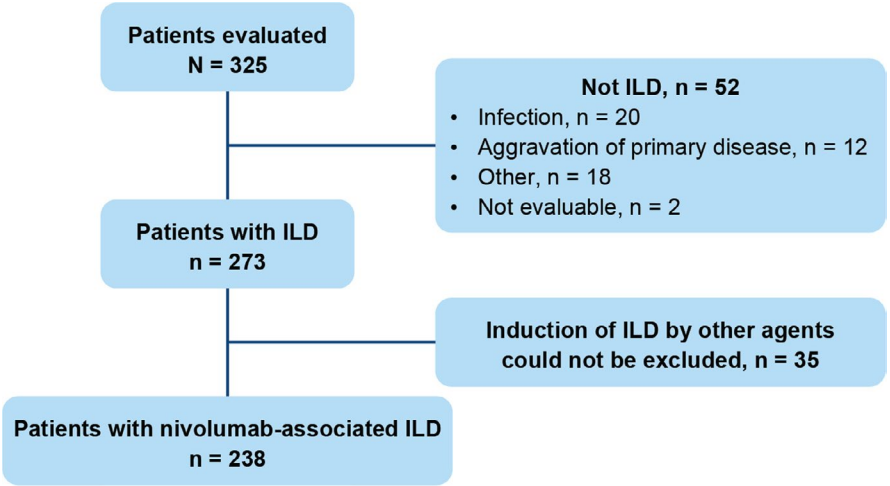

FIGURE 1 Patient disposition (Reprinted from Saito et al. 2020). ILD, interstitial lung disease

TABLE 1 Treatment administered to patients with nivolumab-associated ILD[a]

Treatment, n (%)[b]	All patients (N = 238)	Patients who died of ILD (n = 37)	Patients who survived (n = 201)
Immunosuppressants	0 (0)	0 (0)	0 (0)
Corticosteroids	202 (84.9)	32 (15.8)	170 (84.2)
Immunosuppressants + corticosteroids	5 (2.1)	3 (60.0)	2 (40.0)
Others (eg, antibiotics)	5 (2.1)	1 (20.0)	4 (80.0)
No treatment	26 (10.9)	1 (3.8)	25 (96.2)

Abbreviation: ILD, interstitial lung disease.

[a]Treatment administered for the initial ILD is shown for patients who developed multiple ILD.

[b]Percentages in all patients are based on the total number of patients who experienced nivolumab-induced ILD. Percentages of patients who died of ILD and patients who survived are based on the total number of patients who received each treatment.

TABLE 2 Duration (d) of corticosteroid treatment administered to patients with nivolumab-associated ILD treated with corticosteroids[a]

Duration (d) of corticosteroid treatment, n (%)[b]	All patients treated with corticosteroids (N = 207)	Patients who died of ILD (n = 35)	Patients who survived (n = 172)
<28	104 (50.2)	25 (24.0)	79 (76.0)
≥28	89 (43.0)	6 (6.7)	83 (93.3)
<14	48 (23.2)	15 (31.3)	33 (68.8)
14-27	56 (27.1)	10 (17.9)	46 (82.1)
28-41	27 (13.0)	3 (11.1)	24 (88.9)
42-55	23 (11.1)	2 (8.7)	21 (91.3)
56-69	10 (4.8)	0 (0)	10 (100)
≥70	29 (14.0)	1 (3.4)	28 (96.6)
Unknown	14 (6.8)	4 (28.6)	10 (71.4)

Abbreviation: ILD, interstitial lung disease.

[a]Treatment duration for the initial ILD is shown for patients who developed multiple ILD.

[b]Percentages in all patients are based on the total number of patients who experienced nivolumab-induced ILD. Percentages of patients who died of ILD and who survived are based on the total number of patients who were treated for the respective duration.

3.3 | Relapse of interstitial lung disease

Nine patients experienced a relapse of ILD (Table 4). The median time between recovery from initial ILD and relapse was 53 days (range, 15-279 days). Of the nine patients with relapsed ILD, four patients experienced respiratory failure at initial ILD. Four patients were receiving nivolumab (continuing or restarted) at the time of relapse. At ILD relapse, four patients were no longer being treated, or had never been treated, with corticosteroids for the initial ILD; no data on corticosteroid status were available for one patient. In contrast, four patients were receiving ongoing corticosteroids, and of those, three patients were receiving total daily doses equivalent to prednisolone ≤5 mg. For the treatment of relapse, all patients (except for one patient, whose treatment was unknown) received corticosteroids. At the time of reporting, five patients had recovered, one patient was recovering, one patient had not recovered, and one patient had died. The outcome of the patient with unknown treatment was also unknown. All nine patients had a non–DAD-like radiographic pattern at initial ILD, but of those, one patient who died had a DAD-like pattern before death, which had progressed from a faint infiltration/hypersensitivity pneumonia at the time of relapse.

4 | DISCUSSION

In this post–marketing study, corticosteroids were used for the treatment of nivolumab-induced ILD in more than 80% of patients. This is the first post–marketing study to extensively document the treatment and outcomes of nivolumab-induced ILD in patients with NSCLC in clinical practice in Japan. Most patients responded well to corticosteroid treatment and recovered from ILD. In addition, many patients who experienced a relapse of ILD also responded well to corticosteroids and recovered from the relapse. These results provide real-world evidence that corticosteroids are an effective treatment for nivolumab-induced ILD in patients with NSCLC.

Patients who were treated with corticosteroids responded well to treatment, with 84.2% recovering from ILD; this was consistent with the results from clinical trials. A pooled analysis of two phase II trials (JapicCTII-132072 and JapicCTI-132073), which evaluated

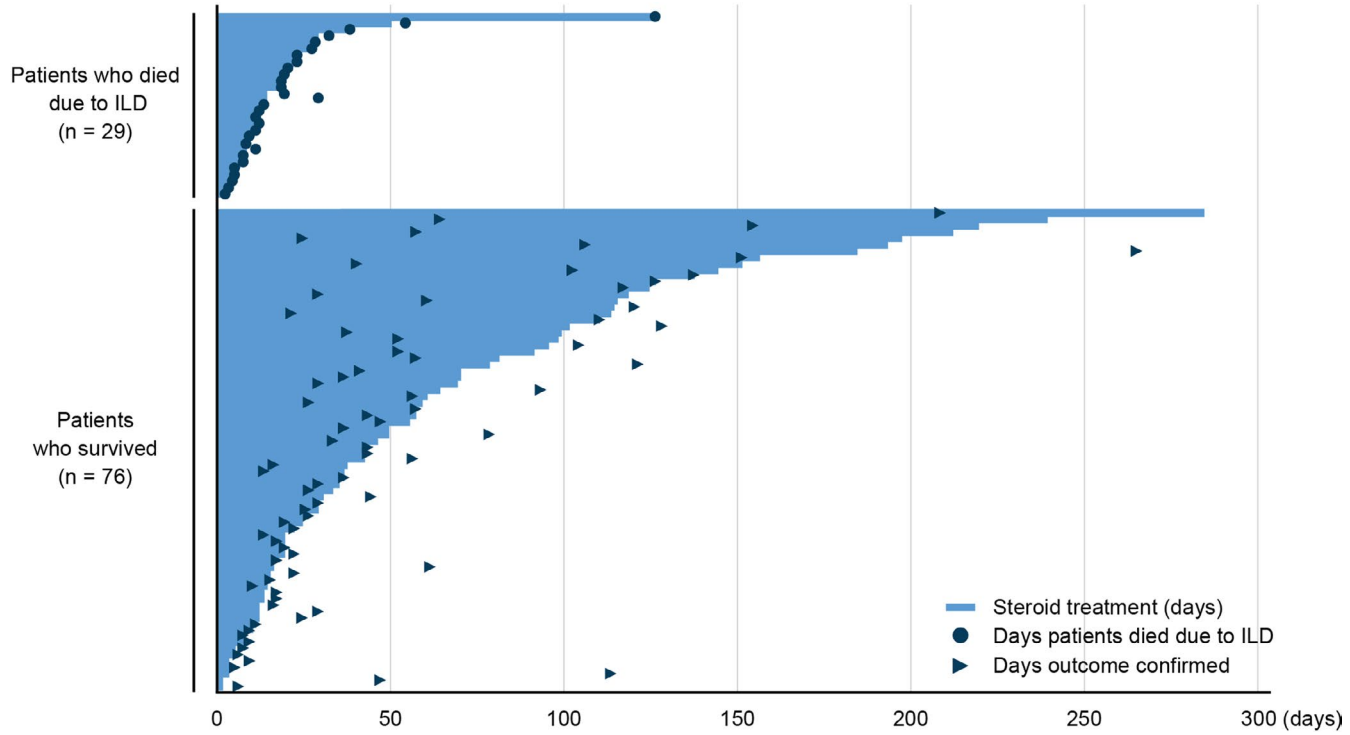

FIGURE 2 Swimmer plot of corticosteroid treatment period of patients who survived and patients who died of ILD; 102 patients were not included because outcomes were recovering or unknown and/or the end dates of corticosteroid treatment were not recorded. ILD, interstitial lung disease

111 nivolumab-treated patients with NSCLC in Japan, reported that eight patients experienced ILD and seven of them were treated with corticosteroids.[1] Of those, 85.7% (6/7) of patients responded well to treatment and recovered from ILD. In the Checkmate 017 trial, six nivolumab-treated NSCLC patients experienced pneumonitis; all five patients who received corticosteroids recovered.[5] The Checkmate 057 trial reported that of the 10 patients who experienced pulmonary AEs (including ILD), seven patients received immunomodulating medications (generally corticosteroids), and all recovered.[2] Furthermore, in the current study, only 15.8% of patients died of ILD following corticosteroid treatment. This was lower than the number of deaths reported in a cohort study of 3166 Japanese patients with NSCLC treated with gefitinib, a tyrosine kinase inhibitor, or chemotherapy, in which the mortality rates were 31.6% and 27.9%, respectively.[6] Therefore, the results from the current study indicate that corticosteroids are effective in treating nivolumab-induced ILD in both the clinical trial and real-world settings.

Better outcomes were reported when patients were treated with corticosteroids and for ≥28 days, although treatment duration and time from ILD onset until death were almost the same in many patients who died of ILD. More deaths were seen in patients who were treated for <28 days than in patients who were treated for ≥28 days. However, this may be because many of the patients died shortly after the onset of ILD. Furthermore, deaths occurred early

TABLE 3 Starting dose (mg/kg/d) of corticosteroids administered to patients with nivolumab-associated ILD treated with corticosteroids[a]

Starting corticosteroid dose, n (%)[b,c]	All patients treated with corticosteroids (N = 207)	Patients who died of ILD (n = 35)	Patients who survived (n = 172)
<0.5 mg/kg/d	47 (22.7)	2 (4.3)	45 (95.7)
≥0.5 to <1.0 mg/kg/d	47 (22.7)	4 (8.5)	43 (91.5)
≥1.0 to <2.0 mg/kg/d	22 (10.6)	9 (40.9)	13 (59.1)
≥2.0 mg/kg/d (excluding pulse therapy)	4 (1.9)	0 (0)	4 (100)
Pulse therapy	87 (42.0)	20 (23.0)	67 (77.0)

Abbreviation: ILD, interstitial lung disease.

[a]Corticosteroid doses administered for the initial ILD are shown for patients who developed multiple ILD.

[b]Doses were converted and reported as prednisolone equivalent doses.

[c]Percentages in all patients are based on the total number of patients who experienced nivolumab-induced ILD. Percentages of patients who died of ILD and who survived are based on the total number of patients who received the respective corticosteroid doses.

TABLE 4 Characteristics of patients who experienced a relapse of ILD

		Initial ILD					Relapse ILD			
Sex/age	Body weight (kg)	Interval from start of NIV to initial ILD (d)	Resp. failure[a]	Starting steroid dose (mg/d)[b]	Steroid treatment (d)	NIV status	Steroid status[b]	Starting steroid dose (mg/d)[b]	Outcome	Change in ILD image pattern[c]
M/67	57.8	115	No	50 mg	94	Disc.	5 mg ongoing	50 mg	Recovered	Others → COP/CEP
M/56	71.0	71	No	30 mg	110	Disc.	4 mg ongoing	20 mg	Recovered	Others → COP/CEP
M/67	44.0	51	Yes	40 mg	126	Disc.	Completed	40 mg	Recovered	COP/CEP (no change)
M/60	70.2	164	Yes	30 mg	70	Disc., restart	Completed	20 mg	Recovered	COP/CEP (no change)
M/55	69.0	10	No	Pulse therapy	256	Disc., restart	35 mg ongoing	Pulse therapy	Death	COP/CEP → Faint infil./HP[d]
M/79	59.0	161	No	100 mg	Unknown (>9)	Disc.	2.5 mg ongoing	30 mg	Recovering	COP/CEP (no change)
F/79	42.0	23	Yes	20 mg	33	Disc., restart, Disc.[e]	Completed	Unknown	Unknown	Others → Faint infil./HP
F/64	58.4	41	No	Not received	—	Disc., restart	No treatment	30 mg	Recovered	COP/CEP (no change)
M/66	50.0	111	Yes	Pulse therapy	>3	Cont.	Unknown	Pulse therapy	Not recovered	COP/CEP (no change)

Abbreviations: CEP, chronic eosinophilic pneumonia; Cont., continued; COP, cryptogenic organizing pneumonia; DAD, diffuse alveolar damage; Disc., discontinued; F, female; Faint infil./HP, faint infiltration/hypersensitivity pneumonia; ILD, interstitial lung disease; M, male; NIV, nivolumab; Resp., respiratory; Restart, restarted.

[a]Respiratory failure was defined as the presence of any respiratory symptoms requiring oxygen administration.

[b]Doses were converted and reported as daily prednisolone equivalent doses.

[c]Change of ILD image pattern from initial ILD to the time of relapse.

[d]ILD image pattern further progressed to DAD-like pattern before death.

[e]Discontinued again for a different reason.

(ie, <28 days of start of treatment) in many patients, even though these patients received treatment in line with the current guidelines.[9,10] These results showed that, although the effect of corticosteroid treatment duration on disease prognosis is still unknown, longer survival was achieved in patients who were treated (or who were able to be treated) with corticosteroids for a longer period. In addition, the pooled analysis discussed above reported a case of death in which corticosteroid therapy was not started at the onset of ILD but was started when ILD exacerbated.[1] The study concluded that immunosuppressive drugs such as corticosteroids should be started in a timely manner to prevent worsening of ILD and death.[1] Furthermore, the manufacturer of nivolumab recommends close monitoring of symptoms to allow early diagnosis, and several guidelines recommend frequent chest examination and pulse oximetry for prompt management.[9,10] Further improvement in the management of nivolumab-induced ILD may also be achieved with early diagnosis and treatment, although additional studies are required to confirm this.

In this study, immunosuppressants other than corticosteroids were used in only five patients. Several guidelines, such as the National Comprehensive Cancer Network guideline, recommend the use of other immunosuppressants in patients who are refractory to corticosteroids; according to these guidelines, infliximab or mycophenolate may be added to corticosteroids if no improvement is seen after 48 hours of corticosteroid treatment.[9,11] The low rate of immunosuppressant use in this study may suggest that most patients responded well to corticosteroids. However, because the data were collected soon after nivolumab was approved for the treatment of NSCLC in Japan, it is possible that physicians took a conservative approach when patients developed ILD by using only corticosteroids to treat the symptoms. Therefore, the use of other immunosuppressants may have become more common in recent years. As illustrated by a recent case report, a dramatic improvement in immune-mediated ILD was observed in a patient with metastatic melanoma following the addition of intravenous infliximab to intravenous methylprednisolone.[12] This study concluded that, although further study may be required, early initiation of immunosuppressants may provide benefit to patients with life-threatening cases of immune-mediated pneumonitis.

This was also the first study to extensively document relapse cases of ILD. At the time of relapse, most patients were either not taking or were taking a low total daily dose of corticosteroids, suggesting that relapse occurs when corticosteroid treatment is nearly completed or stopped. This may be explained by the sustained immunostimulant effect of nivolumab.[13,14] Furthermore, it is known that patients who have ILD and radiographic images with a cryptogenic organizing pneumonia or chronic eosinophilic pneumonia (COP/CEP)–like pattern often experience a relapse, particularly when corticosteroid doses are tapered or discontinued.[15-17] In this study, many patients who experienced a relapse had a COP/CEP-like pattern at initial ILD, suggesting that this relationship between a COP/CEP-like pattern and relapse may also be true in nivolumab-induced ILD. Therefore, it may be particularly important to monitor patients with COP/CEP-like patterns carefully, taking into consideration that they may be prone to a relapse when corticosteroid treatment is being discontinued. At the time of relapse, 44.4% (4/9) of patients were taking nivolumab because they either were restarted after the resolution of the initial ILD or were continuing from the initial ILD; of these four patients, only two recovered. A recent retrospective cohort study also reported that re–treatment with anti–PD-1 therapy resulted in 52% of patients experiencing recurrent or new immune-related AEs.[18] Although the topic of re–treatment is still under discussion for lower grades of ILD,[19] these results suggest that nivolumab should not be continued or restarted unless the benefits outweigh the potential risks. A total of six patients either recovered or were recovering, and there was only one patient who died from a relapse. The patient who died after a relapse had a non–DAD-like pattern at initial ILD and at time of relapse but had progressed to a DAD-like pattern before death. This was consistent with our primary manuscript, which showed that a DAD-like pattern is one of the poor prognostic factors.[8]

The main strength of this study is that it examined patients with NSCLC who were treated with nivolumab and experienced ILD in a real-world setting, and, therefore, the data are generalizable to the Japanese population. This study also had a sufficiently large sample size, and ILD-related data for each patient were carefully assessed by a group of experts to ensure that the ILD experienced by patients was due to nivolumab treatment. However, the study was limited by its post–marketing study design, with the spontaneous reporting of disease status and treatment decisions made by the treating physicians. Therefore, full data for all patients may not have been available. Furthermore, patients had to have clinical findings and radiographic images available to be included in this study, meaning not all cases of nivolumab-associated ILD that occurred in NSCLC patients during the surveillance period were necessarily included.

In conclusion, corticosteroids play an important role in treating ILD following nivolumab treatment in patients with NSCLC. To help prevent relapse (and possible death due to relapse), physicians should be cautious and provide extra care to patients who experience nivolumab-induced ILD, especially when ceasing or reducing the dose of corticosteroids.

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Role of the sponsor

The study sponsors were involved in the study design, writing of the report, and in the decision to submit the article for publication.

Role of contributors

All authors participated in the drafting, critical revision, and approval of the final version of the manuscript. M. Sata, Y. Ito, T. Sakamoto, and K. Kuwano were involved in the study design. M. Sata, S. Sasaki, K. Oikado, Y. Saito, J. Tominaga, F. Sakai, T. Kato, T. Iwasawa, H. Kenmotsu, M. Kusumoto, T. Baba, M. Endo, Y. Fujiwara, H. Sugiura, N. Yanagawa, and K. Kuwano were investigators in the study. Y. Ito and T. Sakamoto conducted the statistical analysis. All authors except Y. Ohe participated in data collection. M. Sata, S. Sasaki, K. Oikado, Y. Saito, J. Tominaga, Y. Ito, T. Sakamoto, Y. Ohe, and K. Kuwano participated in the interpretation of the study results.

CONFLICT OF INTEREST

Y. Saito reports personal fees from AstraZeneca and Ono. K. Oikado reports personal fees from Konica Minolta Precision Medicine Japan, Ono, and Takeda. J. Tominaga, N. Yanagawa, and K. Kuwano report personal fees and/or grants from Ono. M. Sata and F. Sakai report personal fees from AstraZeneca and Ono. T. Kato reports personal fees and/or grants from AbbVie, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eli Lilly, Merck Biopharma, MSD, Nippon Kayaku, Novartis, Ono, Pfizer, Regeneron, Shionogi, Taiho, and Takeda. H. Kenmotsu reports personal fees and/or grants from AstraZeneca, Chugai, and Ono. M. Kusumoto reports personal fees from AstraZeneca, Canon Medical Systems, MSD, and Ono. T. Baba reports personal fees from AstraZeneca, BMS, and Ono. Y. Fujiwara reports grants from AbbVie, Eisai, Eli Lilly, Incyte, and Merck Serono, grants and personal fees from AstraZeneca, BMS, Chugai, Daiichi-Sankyo, MSD, and Novartis, and personal fees from Ono, outside the submitted work. Y. Ito and T. Sakamoto are employed by Ono. Y. Ohe reports personal fees and/or grants from AstraZeneca, BMS, Chugai, MSD, and Ono. M. Endo, T. Iwasawa, S. Sasaki, and H. Sugiura have no conflicts of interest to declare.

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