Received: 8 September 2019 | Accepted: 7 May 2020 | Published on: 5 August 2020

DOI: 10.1111/ajco.13380

REVIEW

WILEY

Programmed cell death 1 (PD-1)/PD-ligand 1(PD-L1) inhibitors-related pneumonitis in patients with advanced non–small cell lung cancer

Yuxin Sun[1] | Chi Shao[1] | Shan Li[1] | Yan Xu[1] | Kai Xu[2] | Ying Zhang[3] | Hui Huang[1] | Mengzhao Wang[1] | Zuojun Xu[1]

[1]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[2]Radiological Department, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

[3]International Medical Service Department, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Correspondence
Hui Huang, MD, Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, #1 Shuaifuyuan Street, Dongcheng District, Beijing, China, 100730
Email: pumchhh@126.com

Yuxin Sun and Chi Shao contributed equally.

Hui Huang and Mengzhao Wang contributed equally.

Funding information
CAMS Innovation Fund for Medical Sciences, Grant/Award Number: 2018-I2M-1-003; Chinese National Natural Science Fund Youth Fund project, Grant/Award Number: 81600050; "13th Five-Year" National Science and Technology Major Project for New Drugs, Grant/Award Number: 2019ZX09734001-002

Abstract

Immune-related pneumonitis is an uncommon but potentially fatal immune-related adverse event in advanced non–small cell lung cancer (NSCLC) patients during treatment with anti-programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1). Underlying emphysema, interstitial lung disease (ILD), and previous radiation therapy for lung cancer might be factors precipitating immune-related pneumonitis. The incidence of immune-related pneumonitis is reported to be higher in those treated with PD-1 inhibitors than in those treated with anti-PD-L1 inhibitors. Early detection and diagnosis and appropriate management according to the severity are critical to improving the prognosis. The first-line physicians, including the primary responsible oncologists, family doctors, emergency physicians and NSCLC patients should be trained to identify and report symptoms of immune-related pneumonitis as early as possible. Multidisciplinary treatment teams involving clinicians (including ILD specialists and lung cancer specialists), radiologists and pathologists are recommended for the treatment of immune-related pneumonitis.

KEYWORDS
immune checkpoint inhibitor, immune-related pneumonitis, non–small cell lung cancer

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs), including anti-programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated-4 (CTLA-4), in monotherapy or in combination, have been shown to be efficacious in the treatment of advanced non–small cell lung cancer (NSCLC).[1,2] However, by activating the immune system against cancer cells, ICIs can also cause immune-related adverse events (irAE). Although it has been reported that the skin, gastrointestinal tract, endocrine glands and liver are the organs/systems most commonly involved in ICI-related irAEs, immune-related pneumonitis can be serious or even potentially life-threatening and can lead to the discontinuation of ICI treatment in NSCLC patients.[3–5] The incidence, clinical manifestations and outcomes of irAE are different between the administration of CTLA-4 and anti-PD-1/PD-L1,[1,6] and it has been reported that immune-related pneumonitis might be more common in patients treated with anti-PD-1/PD-L1 than in those treated with CTLA-4 inhibitors.[6] Immune-related

pneumonitis of any grade and immune-related pneumonitis of grade 3 or higher (≥ grade 3) are more common in immunotherapy for NSCLC than for other malignancies. Anti-PD-1/PD-L1-associated pneumonitis during the treatment of advanced NSCLC is reviewed in detail below.

2 | RISK FACTORS

Although the reported incidence of anti-PD-1/PD-L1-associated pneumonitis varies in different clinical trials, the incidence is less than 10%[7-24] (listed in Table 1). The incidence is not known during immunotherapy for NSCLC in the real world. From the meta-analyses by Khunger et al.[3] and Pallai et al.,[25] the incidence of immune-related pneumonitis is statistically significantly higher in patients receiving PD-1 inhibitors than in those receiving PD-L1 inhibitors, both for any grade or ≥ grade 3 pneumonitis. As we know, both PD-L1 and PD-L2 are ligands for PD-1, however, PD-L2 can bind not only PD-1 but also repulsive guidance molecule b (RGMb). Blockading the RGMb–PD-L2 interaction by anti-PD-L1 might inhibit the development of respiratory tolerance related pneumonitis.[3] It has also been shown in Khunger et al.'s study[3] that the incidence of immune-related pneumonitis is higher for naïve NSCLC patients than for previously treated cases, but there is no difference between the two groups among the patients with ≥grade 3 pneumonitis.

Nivolumab and pembrolizumab are the common PD-1 inhibitors recommended for NSCLC. There is no significant difference in the reported immune-related pneumonitis incidence between them in Khunger et al.'s report.[3] The odds of immune-related pneumonitis are reported to be higher for patients receiving nivolumab plus ipilimumab for the treatment of advanced cancers, including melanoma and NSCLC.[26,27] However, most of the enrolled patients in these studies were melanoma patients. The detailed incidence of immune-related pneumonitis was not analyzed for different cancers, especially for NSCLC. It seems like that there is no obvious difference between the treatment for NSCLC with nivolumab versus nivolumab plus ipilimumab, pembrolizumab versus pembrolizumab plus chemotherapy and atezolizumab versus atezolizumab plus chemotherapy from the listed data in Table 1. There were also no differences in the incidence of immune-related pneumonitis of any grade between patients receiving monotherapy and combination therapy in Cho's cohort.[28] However, Suresh et al. reported that the incidence was higher in NSCLC receiving combination therapy than in those treated with ICI monotherapy.[29] Further sophisticatedly designed studies about different combination therapies for NSCLC are expected in the future.

With the subgroup analyses in the previous studies, patients with squamous cell carcinoma receiving immunotherapy treatment might have a higher incidence of immune-related pneumonitis compared with those with nonsquamous NSCLC receiving immunotherapy.[9,10,29-31] Comorbid emphysema or previous radiation therapy for lung cancer might be precipitating factors for immune-related pneumonitis.[28] However, underlying ILD will increase the risk of immune-related pneumonitis in patients with NSCLC.[28,32-33] Most NSCLC patients with preexisting ILD are always excluded from recent immunotherapy clinical trials. This might be one of the possible causes of the immune-related pneumonitis incidence being lower in phase 3 clinical trials than in phase 1 or 2 trials.[27] There were no significant differences of demographic characteristics, including gender, races and age, between NSCLC cases with or without ICI-ILD receiving PD-1/PD-L1 inhibitors.[29] Smoking is a risk factors for lung cancer, especially for squamous NSCLC. However, the smoking status (current or former or never smoker) was not reported as risk factor for ICI-ILD.[29,34] The prognosis of ICI-ILD was seemed to be worse for current smokers[34] or former smokers.[3]

3 | CLINICAL AND MORPHOLOGICAL MANIFESTATIONS

3.1 | Clinical manifestations

The median time to the onset of immune-related pneumonitis varies in patients taking different immunotherapy agents. The median time to the onset of immune-related pneumonitis was reported by Naidoo to be 2.8 months after the first doses of anti-PD-1/PD-L1,but with a wide range from 9 days to 19.2 months.[34] Delaunay et al. reported that the median duration of ILD-onset after the first dose of anti-PD-1/PD-L1 was 2.1 months, ranging from 0.2 to 27.4 months.[35] It has also been reported to occur as early as hours to days or as late as several months after the first dose, but higher grade pneumonitis occurs within the first 100 to 200 days of immunotherapy.[3] The median time to onset is not correlated with the severity of immune-related pneumonitis.[35] The onset of immune-related pneumonitis is earlier for patients undergoing combination immunotherapy[34]; however, there is no difference between patients receiving anti-PD-1 and anti-PD-L1[35].

The clinical manifestations of immune-related pneumonitis are similar to those of other forms of ILD.[36] Dry cough and exertional dyspnea are the characteristic manifestations. Fever, hemoptysis, chest pain and expectoration are less common. If the pneumonitis is more severe, cyanosis and tachypnea can be observed. As fatigue and rashes are the most common irAEs for anti-PD-1/PD-L1,[5,6,25,37] they might commonly occur concurrently with immune-related pneumonitis. These symptoms are relatively nonspecific and can also be caused by the underlying NSCLC or other immunotherapy-related complications, such as pulmonary infections.

3.2 | Radiological manifestations

High-quality chest CT with standard parameters is essential for the diagnosis of idiopathic pulmonary fibrosis,[36,38] and it is also important for other kinds of ILDs. Chest HRCT is recommended for all NSCLC patients before the first dose of anti-PD-1/PD-L1 and when immune-related pneumonitis is clinically suspected. Contrast CT is usually performed for patients with NSCLC, but it is not a good choice for ILD imaging analysis. On the other hand, repeated HRCT is less harmful and more convenient for NSCLC patients.

TABLE 1 The reported incidence of anti-PD-1/PD-L1-related pneumonitis for NSCLC

Source	ICIs	Lung cancer	Phase	No.	All grade	≥3	ILD-related death
Rizvi, 2015	Nivolumab	NSCLC	2	117	6/5.1%	4/3.4%	0
Gettinger, 2015	Nivolumab	NSCLC	1	129	11/8.5%	4/3.1%	3/2.3%
Brahmer, 2015	Nivolumab	NSCLC	3	131	6/4.6%	0	0
Borghael, 2015	Nivolumab	NSCLC	3	287	4/1.4%	3/1%	0
Garon, 2015	Pembrolizumab	NSCLC	1	495	18/3.6%	9/1.8%	1/0.2%
Herbst, 2016	Pembrolizumab	NSCLC	2/3	690	31/4.5%	14/2.0%	3/0.4%
Reck, 2016	Pembrolizumab	NSCLC	3	154	9/5.8%	4/2.6%	0
Carbone, 2017	Nivolumab	NSCLC	3	267	7/2.6%	4/1.5%	1/0.4%
Mok, 2019	Pembrolizumab	NSCLC	3	636	43/6.8%	20/3.1%	1/0.3%
Reck, 2019	Pembrolizumab	NSCLC	3	154	12/7.8%	4/2.6%	1/0.6%
Fehrenbacher, 2016	Atezolizumab	NSCLC	2	142	4/2.8%	1/0.7%	NA
Rittmeyer, 2017	Atezolizumab	NSCLC	3	425	6/1.4%	4/0.9%	NA
Borghaei, 2019	Pembrolizumab + chemotherapy	Non-squamous NSCLC	3	60	4/6.7%	1/1.7%	0
Gandhi, 2018	Pembrolizumab + chemotherapy	Non-squamous NSCLC	3	704	20/2.8%	13/1.8%	3/0.4%
Paz-Arez, 2018	Pembrolizumab + chemotherapy	Squamous NSCLC	3	109	7/6.4%	3/2.8%	1/0.9%
Socinski, 2018	Atezolizumab+ bevacizumab + chemotherapy	Non-squamous NSCLC	3	356	5/1.3%	4/1.0%	0
West, 2019	Atezolizumab +chemotherapy	Non-squamous NSCLC	3	473	23/4.9%	2/0.4%	NA
Hellmann, 2017	Nivolumab + ipilimumab	NSCLC	1	77	3/3.9%	3/3.9%	0
Hellmann, 2018	Nivolumab + ipilimumab	NSCLC	3	576	22/3.8%	13/2.2%	3/0.5%

PD-1, programmed cell death 1; PD-L1, PD-ligand-1; NSCLC: non–small cell lung cancer; ICIs, immune checkpoint inhibitors; ILD, interstitial lung disease; NA, non applicable.

There is no identified description about the association of the ICI-ILD side and the original tumor side, however, according to Nishino's study, mixed and multifocal distribution of pulmonary shadows in both lower lobes were the common manifestation for ICI-ILD.[39] Consolidation and ground glass opacity (GGO) are the reported CT features of Cho's cases, and consolidation is more common than GGO.[28] GGO, reticular opacities and consolidations were common in patients undergoing nivolumab monotherapy combined with ipilimumab or lirilumab therapy for multiple types of malignancies in Nishino's cohort.[39] The organizing pneumonia (OP) pattern (65%) is the most common CT imaging pattern for lower grade immune-related pneumonitis, followed by the nonspecific interstitial pneumonia pattern (15%).[39] Mixed, nonpure opacities of ground glass infiltrates, consolidation, septal thickening and traction bronchiectasis were observed in Suresh's study.[29] However, the radiographic appearances of immune-related pneumonitis are not specific, vary among patients and may mimic tumor progression or combined pulmonary infection.

3.3 | Pathological manifestations

Surgical biopsy is rarely performed for immune-related pneumonitis, especially in advanced NSCLC patients. Sometimes, transbronchial lung biopsy is performed during the differential diagnosis. However, the specimen harvested through transbronchial lung biopsy is too small and limited to use to obtain a definite pathological pattern for immune-related pneumonitis patients. And lung biopsies will add the risk of acute exacerbation for the ILD, especially for the high-grade ICI-ILD patients. The pathological features are poorly described in the previous anti-PD-1/PD-L1-related trials.

There is no detailed systemic analysis of the pulmonary pathological features of immune-related pneumonitis in NSCLC patients. The few studies of lung biopsies all involve mixed types of advanced cancers[35,34,40] other than NSCLC. On the other hand, there is no specific characteristic pathological manifestations for the ICI-ILD. ICI-ILD, connective tissue disease associated ILD, medications (other than ICI) associated ILD, and so on, can share the similar pulmonary pathological manifestations with idiopathic interstitial pneumonia. So, the pathologist cannot make the diagnosis of ICI-ILD solely according to the pulmonary biopsy without clinical data.

Lung biopsies were performed in 11 cases (41%) at the time of onset of immune-related pneumonitis in the patients in Naidoo et al.'s cohort[34]: eight patients underwent transbronchial lung biopsy, two underwent transbronchial lung cryobiopsy and one underwent wedge resected lung biopsy. Cellular interstitial pneumonitis, OP, diffuse alveolar damage and granulomatous inflammation are common pulmonary pathological manifestations.[34] Inflammation with lymphocyte infiltration was present in the lung tissue obtained by transbronchial lung biopsy in another study for immune-related pneumonitis in patients with different types of underlying cancers.[35]

Nine patients who developed immune-related pneumonitis after treatment with anti-PD-1/PD-L1 for different underlying cancers have been reported recently. Different types of biopsies, including

cryobiopsies (five cases), transbronchial lung biopsies (three cases) and pulmonary autopsy (one case), were performed for these patients. The OP pattern (7 cases), sometimes mixed with vague non-necrotizing granulomas (three among seven cases), is the most common pathological pattern for them. The acute fibrinous pneumonitis pattern and acute and organizing diffuse alveolar damage pattern were observed in the remaining two cases.[40]

4 | DIAGNOSIS AND GRADING

4.1 | Diagnosis

The diagnosis of immune-related pneumonitis is a diagnosis made by exclusion. It is established on the basis of compatible clinical and radiological manifestations, supported by the pulmonary pathological and pathogenic findings in the absence of malignancy and/or infections. New onset or the exaggeration of respiratory manifestations, especially of dry cough, dyspnea, a decrease in oxygen saturation (easily measured by a finger pulse oxygen saturation detector) after immunotherapy with anti-PD-1/PD-L1 for NSCLC, immune-related pneumonitis should be considered.[34]

Pulmonary infections, pulmonary interstitial edema because of heart failure, cancerous lymphangitis, progression of the underlying lung cancer, diffuse alveolar hemorrhage, and pulmonary embolism are the common differential diagnosis. Pulmonary infections, especially opportunistic infections including pneumocystis pneumonia, CMV pneumonia, aspergillosis and mycobacteria pneumonia, are the foremost differential diagnoses for immune-related pneumonitis during the treatment of NSCLC.[34,41–43] On the other hand, corticosteroids and/or other immune-related pneumonitis treatments are also risk factors for complicated pulmonary infections. When pulmonary infection is highly suspected, bronchoscopy is recommended. The pathogen analysis of bronchial secretions or bronchoalveolar lavage fluid will supply important guidance in the diagnosis of pulmonary infections. However, when patients need high levels of oxygen supplementation, it is difficult to perform bronchoscopy.

The development of local, national and international multidisciplinary toxicity teams is suggested for the treatment of irAEs.[44] Multidisciplinary discussion (MDD) involving clinicians, radiologists and pathologists is recommended for the diagnosis and treatment of idiopathic interstitial pneumonia and all types of ILDs.[45] The MDD model is also recommended for the diagnosis and treatment of immune-related pneumonitis during immunotherapy for NSCLC. Pulmonologists specializing in ILD and medical oncologists should be the clinicians involved in the diagnosis and management of immune-related pneumonitis. The early detection and diagnosis of immune-related pneumonitis in patients undergoing treatment with anti-PD-1/PD-L1 is crucial for the treatment of irAEs. To avoid a delay in the diagnosis, all involved first-line physicians, including the primary responsible oncologists, family doctors and emergency physicians and patients and/or their families should be trained to identify and report the related symptoms as early as possible.[46]

4.2 | Severity

The treatment recommendations are based on the severity of immune-related pneumonitis.[41,46] However, there are pulmonary function impairments due to the underlying advanced NSCLC.

For the mild/grade 1 patients, (1) the symptoms are mild or absent, and there is no increased need for oxygen. (2) The new-onset pulmonary infiltration is localized in one lobe or less than 25% of the lung.

For the moderate/grade 2 patients, (1) they are symptomatic and complain of dyspnea (sometimes exertional dyspnea). Most of these patients need additional oxygen. (2) The new-onset pulmonary infiltration is less than 50% of the lung.

For the severe/≥grade 3 patients, (1) obvious dyspnea is the main complaint, and severe hypoxia is common. Invasive or noninvasive respiratory ventilation, such as BiPAP or high-flow nasal cannula oxygen supplementation, should be considered for these patients. (2) The new-onset pulmonary infiltration is more than 50% of the lung.

4.3 | Management

Prevention, detection, monitoring and treatment compose the management of immune-related pneumonitis. Most cases of pneumonitis are mild and asymptomatic, and the daily detection of pulse oxygen saturation at rest and while moving and the timely repetition of chest CT scans are recommended for these patients.[34,46] Anti-PD-1/PD-L1 treatment should be suspended when immune-related pneumonitis is diagnosed in patients with NSCLC. In cases in which severe immune-related pneumonitis is strongly suspected on the basis of clinical and radiological manifestations, treatment should be initiated without pathological evaluation.[42]

Corticosteroids are the most commonly prescribed medications for immune-related pneumonitis. Other immunosuppressants, such as cyclophosphamide, mycophenolate mofetil or infliximab, are administered in severe cases with higher grades.[3,41-42] Intravenous injection (IV) immunoglobin is reported to be an add-on rescue medication.[47] Anti-IL-6, tocilizumab, is reported to be effective for those with refractory immune-related pneumonitis or those in whom initial corticosteroid treatment fails.[48]

For mild/grade 1 cases, clinical monitoring and pulse oxygen saturation detection are more important than treatment, and corticosteroids are not essential for most cases. In addition, the anti-PD-1/anti-PD-L1 treatment is not necessarily discontinued in all mild cases, and the anti-PD-1/anti-PD-L1 treatment might be restarted after the remission of the immune-related pneumonitis. If the clinical symptoms and oxygen saturation are stable, chest CT can be repeated at least every 3–4 weeks.[41–42,46] If not, chest CT should be arranged for them as soon as possible to detect the exacerbation of immune-related pneumonitis.

For the moderate/grade 2 cases, the anti-PD-1/anti-PD-L1 treatment should be withheld immediately, and corticosteroids with the initial dosage of the equivalent of prednisone 1 mg/kg/d should be administered. The patients should be monitored and assessed every 2–7 days. If the clinical condition and/or oxygenation is not improved

in 48–72 hours, a more aggressive treatment should be considered, for example, increasing the dosage of the corticosteroids and adding another immunosuppressant or anti-TNF-α.[41,46] The dosage of corticosteroids can be tapered in 4–6 weeks if the patient has improved. The anti-PD-1/anti-PD-L1 treatment could be restarted if the pneumonitis is stable or has improved with prednisone 10 mg/day. With the reinitiation of anti-PD-1/PD-L1 treatment, the clinical manifestations and oxygenation level should be monitored daily. If refractory immune-related pneumonitis is suspected, the anti-PD-1/anti-PD-L1 treatment should be stopped as soon as possible.

For the severe/≥grade 3 cases, the anti-PD-1/anti-PD-L1 treatment should be stopped immediately. High dosage Intravenous injection (IV) corticosteroids, such as methylprednisolone intravenously 2–4 mg/kg/day can be prescribed. The severity of pneumonitis should be assessed 48–74 hours later. If it has not improved, another immunosuppressant or anti-TNF-α should be added.[41,46] IV immunoglobulin (IVIG) might be an add-on rescue choice.[47] The corticosteroids can be tapered if the patient remains stable or improved for at least 6–8 weeks. The same type of ICI should not be reinitiated.[42,46] Opportunistic infections should be monitored during treatment with corticosteroids and other immunosuppressants. During the administration of corticosteroids, calcium and vitamin D supplementation are recommended.

In summary, immune-related pneumonitis is an uncommon but potentially fatal irAE in patients with NSCLC undergoing treatment with anti-PD-1/PD-L1. The incidence of immune-related pneumonitis is significantly higher in patients treated with PD-1 inhibitors compared with those treated with PD-L1 inhibitors. Comorbid emphysema, ILD and previous radiation therapy for lung cancer might be precipitating factors for immune-related pneumonitis. Monitoring, early detection and diagnosis and appropriate management according to the severity are critical to improving the prognosis for these patients. Both the involved first-line physicians and NSCLC patients should be trained to identify and report symptoms of immune-related pneumonitis as early as possible.

ACKNOWLEDGEMENTS

This work was supported by the Chinese National Natural Science Fund Youth Fund project (grant no. 81600050), "13th Five-Year" National Science and Technology Major Project for New Drugs (grant no. 2019ZX09734001-002), the CAMS Innovation Fund for Medical Sciences (grant no. 2018-I2M-1-003) and this study was supported by CAPTRA Immunotherapy and Immune-Related Adverse Events management platform.

CONFLICTS OF INTEREST

No authors report any conflicts of interest.

ORCID

Hui Huang https://orcid.org/0000-0001-7184-0005

REFERENCES

1. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158–168.
2. Rassy E, Mezquita L, Remon J, Besse B. Non-small-cell lung cancer: What are the benefits and challenges of treating it with immunecheckpoint inhibitors. *Immunotherapy*. 2019;11:1149–1160.
3. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1inhibitors in non-small cell lung cancer: Asystematic review and meta-analysis of trials. *Chest*. 2017;152:271–281.
4. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. *JAMA Oncol*. 2016;2:1346–1353.
5. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: A systematic review and meta-analysis. *JAMA Oncol*. 2019;5:1008–1019.
6. Mantia CM, Buchbinder EI. Immunotherapy toxicity. *Hematol Oncol Clin North Am*. 2019;33:275–290.
7. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018–2028.
8. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small cell lung cancer (CheckMate 063): A phase 2, single-arm trial. *Lancet Oncol*. 2015;16:257–265.
9. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
10. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
11. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
12. Herbst RS, Baas P, Kim DW, et al. Pembrolizumabversus docetaxelfor treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet*. 2016;387:1540–1550.
13. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxelforpatients with previously treated non-small-cell lung cancer (POPLAR): A multicenter, open label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837–1846.
14. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376:2415–2426.
15. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open label, multicentre randomised controlled trial. *Lancet*. 2017;389:255–265.
16. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer(CheckMate 012): Results of an open-label, phase 1, multicohort study. *Lancet Oncol*. 2017;18:31–41.
17. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumabin lung cancer with high tumor mutational burden. *N Engl J Med*. 2018;378:2093–2104.
18. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.
19. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.

20. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
21. Borghaei H, Langer CJ, Gadgeel S, et al. 24-Month overall survival from KEYNOTE -021 cohort G: Pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non-small cell lung cancer. *J Thorac Oncol*. 2019;14:124–129.
22. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locallyadvanced-metastatic non-small-cell lung cancer (KEYNOTE-042): A randomized, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819–1830.
23. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patient with previously treated advanced non-small-cell lung cancer. *J Clin Oncol*. 2015;33:2004–2012.
24. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxelchemotherapy compared with carboplatin plus nab-paclitaxelchemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): A multicenter, randomized, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924–937.
25. Pillai RN, Behera M, Owonikoko TK, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature. *Cancer*. 2018;124:271–277.
26. Huang Y, Fan H, Li N, Du J. Risk of immune-related pneumonitis for PD1/PD-L1 inhibitors: Systematic review and network meta-analysis. *Cancer Med*. 2019;8:2664–2674.
27. 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;2:1607–1616.
28. Cho JY, Kim J, Lee JS, et al. Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. *Lung Cancer*. 2018;125:150–156.
29. Suresh K, Voong KR, Shankar B, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: Incidence and risk factors. *J Thorac Oncol*. 2018;13:1930–1939.
30. Nishino M, Chambers ES, Chong CR, et al. Anti-PD-1 inhibitor-related pneumonitis in non-small cell lung cancer. *Cancer Immunol Res*. 2016;4:289–293.
31. Suresh K, Naidoo J, Lin CT, Danoff S. Immune checkpoint immunotherapy for non-small cell lung cancer: Benefits and pulmonary toxicities. *Chest*. 2018;154:1416–1423.
32. Yamaguchi T, Shimizu J, Hasegawa T, et al. Pre-existing pulmonary fibrosis is a risk factor for anti-PD-1-related pneumonitis in patients with non-small cell lung cancer: A retrospective analysis. *Lung Cancer*. 2018;125:212–217.
33. Kanai O, Kim YH, Demura Y, et al. Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease. *Thorac Cancer*. 2018;9:847-855.
34. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017;35:709–717.
35. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J*. 2017;50:pii: 1700050.
36. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1antibody therapy. *Cancer Treat Rev*. 2016;45:7–18.
37. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplineary consensus classification of the Idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2002;165:277–304.
38. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:e44–e68.
39. Nishino M, Ramaiya NH, Awad MM, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: Radiographic patterns and clinical course. *Clin Cancer Res*. 2016;22:6051–6060.
40. Larsen BT, Chae JM, Dixit AS, Hartman TE, Peikert T, Roden AC. Clinical and histopathologic features of immune checkpoint inhibitor-related pneumonitis. *Am J Surg Pathol*. 2019;43:1331–1340.
41. Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: eSMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(s4):iv119–42.
42. Rashdan S, Minna JD, Gerber DE. Diagnosis and management of pulmonary toxicity associated with cancer immunotherapy. *Lancet Respir Med*. 2018;6:472–478.
43. Picchi H, Mateus C, Chouaid C, et al. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: Reactivation of tuberculosis after anti-PD-1 treatment. *Clin Microbiol Infect*. 2018;24:216–218.
44. Naidoo J, Zhang J, Lipson EJ, et al. A multidisciplinary toxicity team for cancer immunotherapy-related adverse events. *J Natl Compr Canc Netw*. 2019;17:712–720.
45. Travis WD, Costabel U, Hansell DM, 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;188:733–748.
46. Gubens MA, Davies M. NCCN guideline updates: new immunotherapy strategies for improving outcomes in non-small cell lung cancer. *J Natl Compr Canc Netw*. 2019;17(5.5):574–578.
47. Petri CR, Patell R, Batalini F, Rangachari D, Hallowell RW. Severe pulmonary toxicity from immune checkpoint inhibitor treated successfully with intravenous immunoglobulin: Case report and review of the literature. *Respir Med Case Rep*. 2019;27:100834.
48. Stroud CR, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract*. 2019;25:551–557.

How to cite this article: Sun Y, Shao C, Li S, et al. Programmed cell death 1 (PD-1)/PD- ligand 1(PD-L1) inhibitors-related pneumonitis in patients with advanced non-small cell lung cancer. *Asia-Pac J Clin Oncol*. 2020;16:299–304. https://doi.org/10.1111/ajco.13380