REVIEW

The mechanism and risk factors for immune checkpoint inhibitor pneumonitis in non-small cell lung cancer patients

Xiaoyang Zhai¹*, Jian Zhang²*, Yaru Tian¹³, Ji Li¹, Wang Jing¹, Hongbo Guo², Hui Zhu¹
¹Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China; ²Department of Thoracic Surgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, China; ³Department of Radiation Oncology, Shandong Cancer Hospital and Institute affiliated with Shandong University, Jinan 250012, China

ABSTRACT Immune checkpoint inhibitors (ICIs) are new and promising therapeutic agents for non-small cell lung cancer (NSCLC). However, along with demonstrating remarkable efficacy, ICIs can also trigger immune-related adverse events. Checkpoint inhibitor pneumonitis (CIP) has been reported to have a morbidity rate of 3% to 5% and a mortality rate of 10% to 17%. Moreover, the incidence of CIP in NSCLC is higher than that in other tumor types, reaching 7% to 13%. With the increased use of ICIs in NSCLC, CIP has drawn extensive attention from oncologists and cancer researchers. Identifying high risk factors for CIP and the potential mechanism of CIP are key points in preventing and monitoring serious adverse events. In this review, the results of our analysis and summary of previous studies suggested that the risk factors for CIP may include previous lung disease, prior thoracic irradiation, and combinations with other drugs. Our review also explored potential mechanisms closely related to CIP, including increased T cell activity against associated antigens in tumor and normal tissues, preexisting autoantibodies, and inflammatory cytokines.

KEYWORDS Immune checkpoint inhibitor; non-small-cell lung cancer; pneumonitis; risk factors

Introduction Lung cancer has the highest morbidity and mortality rates of malignant tumors, with over 2.09 million diagnosed cases and 1.76 million deaths estimated in 2018¹². Non-small cell lung cancer (NSCLC) is the most common histological type and has a poor prognosis because most patients are diagnosed at an advanced stage³⁶. The 5-year survival rate for advanced NSCLC is only 2.8%⁷. Immune checkpoint inhibitors (ICIs) are promising new immunotherapeutic drugs that reactivate T cells to kill tumor cells by blocking programmed cell death protein 1/ligand 1 (PD-1/PD-L1) pathway or the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) pathway. A growing number of studies have indicated that ICIs can improve the clinical outcomes of advanced NSCLC⁸⁹, ICIs can achieve a 5-year overall survival (OS) rate of 23.2% when used as first-line therapy. For patients with PD-L1 tumor proportion score (PD-L1-positive tumor cells/total number of viable tumor cells) of 50% or greater, the 5-year OS rate can reach 29.6%10. Based on these results, ICIs have been approved as first-line therapies for advanced NSCLC by the US Food and Drug Administration (FDA). However, along with providing an excellent survival benefit, ICIs can also induce specific hyperactivation of the immune response, resulting in normal tissue damage¹¹¹². Immune-related adverse events (irAEs), such as rash, colitis, hepatitis, myocarditis, endocrinopathies, and pneumonitis, are commonly reported¹³. Pneumonitis, termed checkpoint inhibitor pneumonitis (CIP), is particularly worrisome among the irAEs¹⁴¹⁶. Although the incidence of CIP has been reported to be 3% to 5%, it has a fatality rate of 10% to 17%. However, in NSCLC, the morbidity of CIP is 7% to 13%¹⁵¹⁷²². CIP occurs mainly in the first 6 months after treatment¹⁴. The major symptoms are dyspnea, cough, fever, and chest pain³⁴. High-resolution computed tomography is the preferred diagnostic method when CIP is suspected²⁴²⁵. The traditional treatment for CIP is corticosteroid administration.

*These authors contributed equally to this work.
Correspondence to: Hongbo Guo and Hui Zhu
E-mail: guomutong@126.com and drzhuh@126.com
Received March 30, 2020; accepted May 27, 2020.
Available at www.cancerbiomed.org
©2020 Cancer Biology & Medicine. Creative Commons Attribution-NonCommercial 4.0 International License
Additional immunosuppressive agents are necessary for steroid-refractory pneumonitis. However, current studies on CIP have mainly focused on the incidence, diagnosis, and management of this adverse event. Studies concerning the risk factors for CIP are limited. In this study, we reviewed the potential mechanisms and risk factors for CIP in NSCLC patients with the aim of identifying patients with a high probability of CIP, to ensure close monitoring during the course of immunotherapy treatments.

**Mechanism of CIP**

The mechanism of CIP remains unclear, but it is believed to be related to the immune dysregulation caused by ICIs. Postow et al. suggested four potential mechanisms underlying irAEs. First, the occurrence of adverse events may be related to increased T cell activity against cross-antigens expressed in tumor and normal tissues. Suresh et al. found that bronchoalveolar lavage (BAL) samples from CIP patients exhibited increased lymphocytosis, mainly composed of CD4+ T cells. Importantly, the authors observed increased central memory T cell (Tcm) numbers and decreased CTLA-4 and PD-1 expressions within the Treg population. PD-1+ and CTLA-4+ Tregs have negative regulatory effects on CD8+ T cells, conventional T cells (such as Tcms), and macrophage proinflammatory responses. Therefore, increasing activated alveolar T cell numbers and attenuating the anti-inflammatory Treg phenotype may lead to dysregulation of T cell activity. In the tumor microenvironment, reactivated tumor infiltrating lymphocytes (TILs) have the potential to provide an accurate prognosis for NSCLC patients. A meta-analysis of 8,600 patients with lung cancer indicated that a high level of CD8+ T cell infiltration in the tumor nest and tumor stroma, and CD4+ T cell infiltration in the tumor stroma showed better survival. Conversely, a high level of FOXP3+ Tregs in the tumor stroma was related to poor outcomes. Another meta-analysis of NSCLC obtained similar results and showed that TILs had a predictive role for OS and recurrence. Although lymphocytosis was observed in BAL samples from CIP patients, its predictive value of CIP lacks sufficient evidence, and the potential relationship between these parameters needs future exploration. Second, increased levels of preexisting autoantibodies may also be responsible for irAEs. Recent studies have shown that preexisting anti-rheumatoid factor antibodies, antinuclear antibodies, anti-thyroglobulin antibodies, and anti-thyroid peroxidase antibodies are potentially related to the development of irAEs in NSCLC patients. However, unlike the predictive role of preexisting rheumatoid factor in skin reactions and preexisting anti-thyroid antibodies in thyroid dysfunction, the specific antibodies related to CIP are still being explored. Third, increases in the levels of inflammatory cytokines are also related to the appearance of irAEs. An NSCLC patient who developed CIP after atezolizumab treatment was reported to have elevated levels of C-reactive protein and interleukin-6 (IL-6), when compared with baseline levels. Cytokines can also serve as biomarkers for adverse events, and their elevated expression correlates with severe ICI toxicity. The fourth possible mechanism is that anti-CTLA-4 antibodies can directly bind with CTLA-4 expressed on normal tissues, such as the pituitary gland. This mechanism may also be the reason why pituitary inflammation is a specific adverse event of anti-CTLA-4 antibodies. According to the results of these studies, we speculate that the first three mechanisms may be the major causes of CIP, which are summarized in Figure 1. Additional potential mechanisms still require further exploration and verification.

**Risk factors for CIP**

To date, the incidence of CIP is approximately 5% for any grade and 1% for grade 3 or higher pneumonitis in patients treated with anti-PD-1/PD-L1 antibodies. With the widespread application of ICIs, the incidence is expected to increase. A study showed that prior lung disease, prior thoracic radiotherapy, and prior combination therapy were significant risk factors for pneumonitis (odds ratios: 2.86, 3.34, and 2.73, respectively). Moreover, other potential risk factors for CIP include previous or current smoking, an age older than 70 years, PD-1 inhibitor treatment, and histological type. Reviews on risk factors for CIP will facilitate an early diagnosis and management of high risk groups. The detailed risk factors are listed in Table 1.

**Previous lung disease**

Previous lung diseases associated with CIP may include chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease (ILD), pulmonary fibrosis, pneumothorax, and pleural effusion. The incidences of CIP in patients with COPD and asthma were reported to be 2.3% higher than that in patients without COPD and asthma. Additionally, a history of smoking may augment the pneumonitis incidence...
in asthma patients\cite{41}. The leading reasons may be the decline in pulmonary function and poor resistance to outside factors in COPD and asthma patients. However, recent studies have reported that the numbers of CD4+ cells with PD-1 expression increased in COPD patients\cite{42-44}. Therefore, patients with mild COPD may have a higher morbidity of CIP but a longer progression-free survival (PFS) than those without COPD when using ICIs. In a retrospective study enrolling 216 NSCLC

**Table 1** Potential risk factors for checkpoint inhibitor pneumonitis in NSCLC

| Risk factors                        | Details                                                                                                                                 |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Previous lung disease               | COPD, asthma, ILD, pulmonary fibrosis, pneumothorax, and pleural effusion                                                             |
| Combination therapy                 | Additional immune drugs, targeted drugs, and chemotherapeutic drugs. ICI followed by osimertinib may be associated with severe pneumonitis. This association has not been observed when osimertinib preceded treatment with ICIs or when ICIs were followed by treatment with other EGFR-TKIs |
| Prior thoracic radiation therapy    | The associations among chest-RT type, chest-RT timing, receipt of more than one chest-RT course, and CIP have not been proven                                                                 |
| Smoking status                      | Previous or current smoker                                                                                                             |
| Age                                 | Older than 70 years                                                                                                                      |
| PD-1 inhibitors                     | PD-1 inhibitors, such as pembrolizumab and nivolumab, might be associated with a higher incidence of CIP than other ICIs                                                   |
| Different histological type of NSCLC| Patients with squamous NSCLC have a higher incidence but a lower mortality of CIP than those with adenocarcinoma                                           |

NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; ICIs, immune checkpoint inhibitors; TKIs: tyrosine kinase inhibitors; RT: radiation therapy; PD-1: programmed cell death protein 1.
patients receiving nivolumab, the morbidity of patients with 
preexisting ILD was significantly higher than that of patients 
without ILD (31% vs. 12%; \( P = 0.014 \)). Interstitial pulmo-

nary fibrosis is a pathogenicity of ILD. A retrospective ana-

lysis showed that preexisting pulmonary fibrosis was closely 
associated with the risk of anti-PD-1 antibody-related pneu-

monitis showed\footnote{A recent retrospective analysis of 188 NSCLC patients 
showed that RT parameters (technique, timing, courses, and 

prior chest-RT dosimetric parameters) were not associated 
with immune-related pneumonitis. Notably, a study showed 
that the incidence of pneumonitis was higher in an RT group 
with curative intent than in an RT group with palliative intent 
(89% vs. 11%; \( P = 0.051 \)). Moreover, the timing of RT is very 
important, and adding RT before or after immunotherapy 
remains controversial. A retrospective review recently found 
that RT following immunotherapy was relevant to improved 
survival. However, this finding could be explained by the 
relatively good general status and the reduced progression in 
patients treated with RT after immunotherapy.}

A recent retrospective analysis of 188 NSCLC patients 
showed that RT parameters (technique, timing, courses, and 

prior chest-RT dosimetric parameters) were not associated 
with immune-related pneumonitis. Notably, a study showed 
that the incidence of pneumonitis was higher in an RT group 
with curative intent than in an RT group with palliative intent 
(89% vs. 11%; \( P = 0.051 \)). Moreover, the timing of RT is very 
important, and adding RT before or after immunotherapy 
remains controversial. A retrospective review recently found 
that RT following immunotherapy was relevant to improved 
survival. However, this finding could be explained by the 
relatively good general status and the reduced progression in 
patients treated with RT after immunotherapy.\footnote{A related radiomics trial is ongoing (NCT03305380), which may offer a new approach for the diagnosis and prediction of CIP.}

It is difficult for clinicians to differentiate whether the cause 
of pneumonitis is related to radiation or immunotherapy. 
Radiation pneumonitis (RP), an early change in radiation-

induced lung injury, usually occurs between 1 and 3 months 
after RT. The median time of CIP onset is 82 days after 
immunotherapy, which is similar to that of RP. The main 
imaging features of the two types of pneumonitis are ground 
glass opacity or diffuse haziness, and the pathological feature 
is lymphocytic alveolitis. However, RP mostly occurs in 
the radioactive field, and CIP is mainly found within the low 
dose range or outside the RT fall-off dose region. Notably, 
although it is difficult to distinguish the two types of pneumo-

nitis in patients previously treated with both treatments, the 
first-line therapy for both is corticosteroids. Radiomics, an 
emerging field, provides a new method to predict immuno-

therapy-induced pneumonitis. This technique automatically 
extracts imaging features from medical imaging data for 
analysis by synthesis. A related radiomics trial is ongoing 
(NCT03305380), which may offer a new approach for the 
diagnosis and prediction of CIP.

**Combination with ICIs or other drugs**

ICIs are usually combined with chemotherapeutic drugs, 


tyrosine kinase inhibitors, or additional immune-targeted 


drugs. In a meta-analysis of 4,496 patients, the incidence 
of pneumonitis in patients treated with a PD-1 inhibitor or 
combination therapy was 2.7% vs. 6.6%, respectively. The 
combination of ICIs and chemotherapy, as a recommended
treatment according to guidelines, is increasingly used in the clinic. Pembrolizumab combined with chemotherapy prolongs the median OS of NSCLC patients by nearly 5 months. However, the incidence of any-grade CIP was found to be increased threefold in a combination group compared with a chemotherapy group\textsuperscript{65}. Notably, in the preclinical phase of the I b TATTON study, the reported incidence was 2.9% for osimertinib monotherapy and 38% for osimertinib combined with durvalumab\textsuperscript{66}. Treatment in the concurrent treatment group was paused because of high rates of pneumonitis. Oshima et al.\textsuperscript{67} also evaluated the incidence of pneumonitis in patients treated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) with or without nivolumab, which produced incidence rates of 25.7% and 4.59%, respectively. Thirteen of 18 cases of pneumonitis treated with both EGFR-TKIs and nivolumab developed after the discontinuation of nivolumab. The average interval time was 71.1 days. In addition to being related to the order of treatment, pneumonitis may be associated with specific TKIs. One recent study showed that the sequential use of PD-(L)1 inhibitors followed by osimertinib within 3 months resulted in more severe irAEs than treatment with osimertinib followed by PD-(L)1 inhibitors or other TKIs following PD-(L)1 blockade\textsuperscript{68}. However, the incidence of pneumonitis following osimertinib monotherapy is higher than that following gefitinib or erlotinib therapy, which was shown in the FLAURA study\textsuperscript{69}. This adverse reaction may be magnified by combination treatment with ICIs. Notably, the treatment modality of osimertinib plus ICIs in clinical practice is limited. Currently, it is widely considered that PD-1/PD-L1 inhibitors have restricted efficacy in patients with mutation types. Regardless of the risk of CIP, the treatment regimen itself is also controversial. A higher incidence of CIP was observed in the double-immune checkpoint inhibitor groups than in the other control groups in the Checkmate 012, Checkmate 227, and Checkmate 568 clinical trials\textsuperscript{70-72}. However, adverse events were tolerated, and no novel toxicities occurred with combination treatment when compared with single treatment\textsuperscript{71}.

In conclusion, with the popular use of combination therapy, the incidence of CIP will inevitably increase. Clinicians must consider a patient’s general condition, degree of disease, times receiving treatment, and the risk of CIP. The incidence of CIP after immunotherapy combined with other drugs is summarized in Table 2. The mechanism underlying the increased incidence of CIP after combination therapy is not clear. The relatively long duration of treatment and relatively increased antigen or cytokine release may account for the increased incidence of adverse reactions. Further studies are still needed to evaluate the safety and high risk factors for combination therapy.

### Other risk factors

The occurrence of CIP may be related to age, smoking history, drug type, treatment history, and histological type. A previous study found that patients older than 70 years of age were more common in a CIP group than a non-CIP group (54.5% vs. 30.3%; \( P = 0.025\))\textsuperscript{79}. This finding can be explained by the decline in pulmonary function and increase in medical complications in the elderly population. A history of smoking is also a risk factor for CIP. Former/current smokers were found to have a higher incidence of pneumonitis than non-smokers (\( P = 0.03\))\textsuperscript{79}. The high incidence of CIP in NSCLC patients may be due to a history of smoking and a consequential decline in pulmonary function\textsuperscript{80}. Notably, sex may also have an association with the occurrence of CIP. Suresh et al.\textsuperscript{14} reported that females had a higher incidence of CIP than males, but the difference was not significant. Although this result has yet to be confirmed, it does provide a direction for further study. In addition, the incidence of any-grade pneumonitis has been found to be significantly higher in patients receiving PD-1 inhibitors than in those receiving PD-L1 inhibitors (\( P = 0.001\))\textsuperscript{21}. This finding may be because anti-PD-1 drugs can affect the PD-L1 and PD-L2 pathways, while anti-PD-L1 drugs can only influence the PD-L1 pathway. However, pembrolizumab and nivolumab have shown no significant difference in causing CIP morbidity\textsuperscript{20}. Treatment-naive patients may have a higher incidence of any-grade pneumonitis than previously treated patients (\( P = 0.03\))\textsuperscript{21}. ICIs have been approved as a first-line treatment for NSCLC; therefore, treatment history should be seriously considered. Notably, patients with squamous histology have a higher incidence but a lower mortality rate of immune-related pneumonitis than those with adenocarcinoma histology (\( P < 0.05\))\textsuperscript{8,9,14,75,76,81}. However, the phenomenon may be determined by the characteristics of the tumor histology itself rather than those of CIP.

The prevalence of patients with the abovementioned primary risk factors is shown in Table 3. Noteworthy, the incidence of CIP between random clinical trials and the real world was distinguishing. In clinical trials, because of strict inclusion criteria, patients with poor general condition were frequently excluded, which led to an underestimated morbidity rate of
Table 2: Incidence of checkpoint inhibitor pneumonitis in NSCLC patients treated with ICIs and other drugs

| ClinicalTrials.gov identifier | Source | Phase | Histological types | Interventions | No. of patients | All-grade pneumonitis (%) | Grade ≥ 3 pneumonitis (%) |
|-----------------------------|--------|-------|--------------------|----------------|-----------------|--------------------------|--------------------------|
| NCT02477826                | CheckMate 227<sup>70</sup> | 3     | NSCLC              | Arm I: nivolumab plus ipilimumab | Arm I: 4% | Arm I: 2% |
|                            |        |       |                    | Arm II: nivolumab plus chemotherapy | Arm II: 2% | Arm II: 2% |
|                            |        |       |                    | Arm III: chemotherapy | Arm III: 1% | Arm III: <1% |
| NCT02659059                | CheckMate 568<sup>72</sup> | 2     | NSCLC              | Nivolumab plus ipilimumab | Nivolumab plus ipilimumab | 6.9% | 2.1% |
| NCT01454102                | CheckMate 012<sup>71</sup> | 1     | NSCLC              | Arm I: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks | Arm I: 5% | Arm I: 5% |
|                            |        |       |                    | Arm II: nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks | Arm II: 3% | Arm II: 3% |
| NCT02039674                | KEYNOTE-021<sup>73</sup> | 1/2   | NSCLC              | Arm I: pembrolizumab plus erlotinib | Arm I: 0% | Arm I: 0% |
|                            |        |       |                    | Arm II: pembrolizumab plus gefitinib | Arm II: 14.3% | Arm II: 0% |
| NCT02454933                | CAURAL<sup>74</sup> | 3     | NSCLC              | Arm I: osimertinib plus durvalumab | Arm I: 17% | Arm I: 0% |
|                            |        |       |                    | Arm II: osimertinib | Arm II: 18% | Arm II: 12% |
| NCT02143466                | TATTON<sup>66</sup> | 1b    | NSCLC              | Arm I: durvalumab | Arm I: 2.0% | Arm I: 0.6% |
|                            |        |       |                    | Arm II: osimertinib plus durvalumab | Arm II: 38% | Arm II: 15% |
| NCT02578680                | KEYNOTE-189<sup>75</sup> | 3     | Non-squamous       | Arm I: pembrolizumab plus chemotherapy | Arm I: 4.4% | Arm I: 2.7% |
|                            |        |       |                    | Arm II: placebo plus chemotherapy | Arm II: 2.5% | Arm II: 2.0% |
| NCT02366143                | IMpower150<sup>76</sup> | 3     | Non-squamous       | Arm I: bevacizumab plus chemotherapy | Arm I: 1.3% | Arm I: 0.5% |
|                            |        |       |                    | Arm II: atezolizumab plus bevacizumab plus chemotherapy | Arm II: 2.8% | Arm II: 1.5% |
| NCT02039674                | KEYNOTE-021<sup>77</sup> | 2     | Non-squamous       | Arm I: pembrolizumab plus chemotherapy | Arm I: 7% | Arm I: 2% |
|                            |        |       |                    | Arm II: chemotherapy | Arm II: 0% | Arm II: 0% |
| NCT02775435                | KEYNOTE-407<sup>65</sup> | 3     | Squamous           | Arm I: pembrolizumab plus chemotherapy | Arm I: 6.5% | Arm I: 2.5% |
|                            |        |       |                    | Arm II: chemotherapy | Arm II: 2.1% | Arm II: 1.1% |
| NCT02367794                | IMpower131<sup>78</sup> | 3     | Squamous           | Arm I: atezolizumab plus chemotherapy | Arm I: 7% | Arm I: 1% |
|                            |        |       |                    | Arm II: chemotherapy | Arm II: 1% | Arm II: 1% |

NSCLC, non-small lung cancer; ICIs: immune checkpoint inhibitors.
Cancer Biol Med Vol 17, No 3 August 2020

CIP. According to a previous report, the incidence of pneumonitis in the real world can reach as high as 19% and was much higher than the pneumonitis rate of 3%–5% reported in clinical trials \(^\text{14}\). With increasing use of ICIs and greater awareness about CIP, the rate of CIP in the real world should be higher in future studies.

### Management of CIP

Guidelines on immunotherapy-related toxicity recommend corticosteroids as the main therapeutic modality for CIP \(^\text{25,83,84}\). If no remission is observed after 48 hours, immunosuppressive agents are recommended. The specific management approach is shown in Figure 2. Retrospective data from a large cohort study showed that 1 out of 10 patients receiving steroid therapy required additional immunosuppressive therapy \(^\text{85}\). However, there is still debate regarding which immunosuppressant to use. Infliximab, a monoclonal anti-tumor necrosis factor-α (TNF-α) antibody, is recommended as the first-line immunosuppressive drug for steroid-refractory CIP. Although NSCLC patients with steroid-refractory CIP have benefited from infliximab \(^\text{86}\), the recommendation is based on extrapolation from the efficacy of infliximab in managing immune-related colitis and lacks pathophysiological support. Notably, infliximab itself can cause interstitial pneumonitis and liver injury \(^\text{87-89}\). As a recommended second-line drug, mycophenolate mofetil (MMF) is still controversial as a treatment for steroid-refractory CIP. The recommendation was mainly based on its efficacy in treating immune-related hepatitis \(^\text{90}\). However, data from patients with ICIs have shown that MMF has negative effects on the T cell response \(^\text{91}\). Many cytokines, including IL-1, IL-6, and TNF-α, are continuously secreted in response to the acute inflammatory phase of CIP \(^\text{91}\). IL-6 and IL-1β have been reported to promote cancer progression and metastases \(^\text{92,93}\). Therefore, without affecting immunotherapy efficacy, IL-6 blockade (tocilizumab), IL-1 blockade (anakinra), and TNF-α blockade (infliximab) may be possible approaches to treat steroid-refractory CIP. An NSCLC patient with immune-related pneumonitis was treated with tocilizumab after the initiation of steroid therapy and showed significant symptomatic relief within

| Trial/author | Phase/real world | Immune checkpoint inhibitor | Risk factor | The incidence of any-grade pneumonitis |
|-------------|------------------|-----------------------------|-------------|--------------------------------------|
|             |                  |                             | With risk factor (%) | Without risk factor (%) |
| Keynote-001 \(^\text{40}\) | Phase 1 | Pembrolizumab | Asthma or COPD | 5.4 | 3.1 |
| Galant-Swafford et al. \(^\text{41}\) | Real world | Mainly nivolumab or pembrolizumab | Asthma | 11.5 | 4.3 |
| Kanai et al. \(^\text{45}\) | Real world | Nivolumab | ILD | 31 | 12 |
| Shibaki et al. \(^\text{82}\) | Real world | Nivolumab or pembrolizumab | ILD | 29 | 10 |
| Yamaguchi et al. \(^\text{46}\) | Real world | Nivolumab or pembrolizumab | Pulmonary fibrosis | 35.1 | 5.8 |
| Keynote-001 \(^\text{55}\) | Phase 1 | Pembrolizumab | Thoracic radiotherapy | 13 | 1 |
| Voong et al. \(^\text{58}\) | Real world | Mainly nivolumab or pembrolizumab | Thoracic radiotherapy | 19 | 19 |
| Keynote-407 \(^\text{65}\) | Phase 3 | Pembrolizumab | Combination with chemotherapy | 6.5 | 2.1 |
| TATTON \(^\text{56}\) | Phase 1b | Durvalumab | Combination with osimertinib | 38 | 2.9 |
| CAURAL \(^\text{74}\) | Phase 3 | Durvalumab | Combination with osimertinib | 17 | 18 |
| Oshima et al. \(^\text{57}\) | Real world | Nivolumab | Combination with targeted TKI | 25.7 | 4.6 |
| Checkmate 227 \(^\text{70}\) | Phase 3 | Nivolumab plus pembrolizumab | Double-immune checkpoint inhibitors | 4 | 1 |

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; TKI, tyrosine kinase inhibitor.
2 days of hospitalization. However, the efficacy and safety of these agents still require further investigation.

### Predictive factors of CIP

In NSCLC, the prevalence of CIP is 7% to 13%. With increasing application, the incidence may increase. However, predictive factors regarding CIP are still being explored. The potential predictive factors reported to date have mainly focused on cellular biomarkers and cytokines/chemokines. A retrospective study of 101 patients with melanoma indicated that increased white blood cell counts and decreased relative lymphocyte counts correlated with G3/4 lung and gastrointestinal irAEs. Another study also showed that higher baseline lymphocyte counts were associated with irAEs in solid tumors. In melanoma patients with severe irAEs, peripheral blood samples were evaluated at an early time point during treatment, and 11 elevated cytokines were noted, including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, fractalkine, fibroblast growth factor 2, IFN-a, interleukin-12p70, IL-1a, IL-1b, IL-1 receptor antagonist, IL-2, and IL-13. A predictive model composed of these 11 cytokines was verified in a validation group.

### Future directions for CIP

Although ICIs have been approved as first- and second-line treatments for multiple solid tumors, many questions remain. First, the ability of biomarkers to predict irAEs is still unclear. The present biomarkers are mostly related to the mechanism of occurrence of irAEs. Clinicians can detect and manage adverse events earlier by evaluating these biomarkers. Second, the relationships between the development of CIP and tumor response or OS remain controversial. Most studies have indicated that NSCLC patients with irAEs have an improved prognosis. However, there is now emerging evidence that the development of CIP, unlike that of other irAEs, is associated with decreased treatment efficacy and survival in ICI-treated NSCLC patients. Notably, the results regarding this topic were all from retrospective analyses, which were inevitably influenced by bias even after statistical adjustment. Therefore, this issue still needs evaluation in prospective and large sample studies. Third, the morbidity and mortality of CIP in diverse NSCLC histological types are confusing. Differences may be related to the intrinsic characteristics of tumor histological types.
Radiation recall pneumonitis after immunotherapy should be considered

Radiation recall pneumonitis (RRP) is acute inflammation triggered by certain pharmacological agents in previously irradiated areas\textsuperscript{103}. The mechanisms of RRP are still unclear. Potential hypotheses involve damage to stem cells in the irradiated area and hypersensitivity of renewed cells\textsuperscript{104,105}. Cases of RRP have been reported after chemotherapy and targeted therapy\textsuperscript{106-108}. The incidence of EGFR-related RRP is 4.4%, yet the incidence of RRP in patients who received targeted therapy within 90 days after radiotherapy was tenfold higher than that in patients who received targeted therapy more than 90 days after radiotherapy\textsuperscript{106}. The median time interval between the end of RT and the initiation of RRP induced by cytotoxic drugs or TKI drugs was 95 days and 124 days, respectively, as previously reported\textsuperscript{106,107}. Immunotherapy, as an emerging therapeutic option, can also induce RRP. Two patients treated with nivolumab were reported to suffer from RRP within two years of radiotherapy completion, which is different from the windows for chemotherapy and targeted therapy\textsuperscript{109}. RRP triggered by pembrolizumab has also been detailed in one case report\textsuperscript{110}. Oncologists should be alert for RRP when radiological findings occur in irradiated areas following the application of drugs. Based on clinical experience, RRP is currently considered to be sensitive to steroids. The model of RT plus immunotherapy will be increasingly used in the clinic based on the PACIFIC study, and RRP needs to be given more attention. Moreover, distant toxicity induced by RT after immunotherapy is also noteworthy. The abscopal effect from immunotherapy combination with radiotherapy refers to tumor regression in a non-irradiated site\textsuperscript{111}. One SCLC patient received peripancreatic radiotherapy after nivolumab and developed bilateral CIP\textsuperscript{112}, which suggested that the mechanism related to the abscopal effect may also trigger immune-related adverse events in nonirradiated sites.

Conclusions

CIP is an immune-related adverse event with relatively low morbidity and high mortality, which is relatively common in NSCLC patients. With the extensive use of ICIs in NSCLC, CIP has attracted widespread attention. Although the mechanism of CIP is still unclear, it is certain that immune dysfunction plays an important role in the development of irAEs. The risk factors for CIP are older age, female sex, history of smoking, histological type associated with CIP, previous lung disease, prior thoracic irradiation, and treatment combinations with other drugs. Patients with these risk factors should be monitored for CIP when using ICIs. In terms of management, current guidelines have provided recommendations for CIP\textsuperscript{113}. However, many questions remain, including screening biomarkers to predict the safety of ICIs, the relationship between the severity of adverse events and the effectiveness of immunotherapy, and the differences among diverse tumor histological types in CIP morbidity and mortality. These challenges need to be addressed in future clinical and preclinical studies. Moreover, because the current guidelines are based mainly on clinical experience and expert consensus, some recommendations remain controversial. Therefore, translation of preclinical data into clinical treatment and the development of guidelines supported by powerful evidence are essential.

Acknowledgments

This work was supported by a grant from the Wu Jieping Medical Foundation (Grant No. 320675018288).

Conflict of interest statement

No potential conflicts of interest are disclosed.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68: 394-424.
2. Lung Cancer Fact Sheet of the Global Health Observatory. http://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed 9 June 2019.
3. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. J Am Med Assoc. 2014; 311: 1998-2006.
4. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006; 355: 2542-50.
5. American Cancer Society. https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed 10 February 2020.
6. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008; 359: 1367-80.
7. Ozkaya S, Fındık S, Dırıcan A, Atıcı AG. Long-term survival rates of patients with stage IIIIB and IV non-small cell lung cancer treated with cisplatin plus vinorelbine or gemcitabine. Exp Ther Med. 2012; 4: 1035-8.
8. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015; 373: 123-35.
9. Reck M, Rodríguez-Abruña D, Robinson AG, Hui R, Cossetti T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016; 375: 1823-33.
10. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-year overall survival for patients with advanced nonsmall-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. J Clin Oncol. 2019; 37: 2518-27.
11. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The relative risk and incidence of immune checkpoint inhibitors related pneumonitis in patients with advanced cancer: a meta-analysis. Front Pharmacol. 2018; 9: 1430.
12. Kooijman VH, Glatz K, Bübendorf L, Weber A, Gaspert A, Cathomas G, et al. [The pathology of adverse events with immune checkpoint inhibitors]. Patholologie. 2017; 38: 197-208.
13. 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.
14. Suresh K, Voong KR, Shankar B, Forde PM, Ettinger DS, Marrone KA, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. J Thorac Oncol. 2018; 13: 1930-9.
15. Suresh K, Naidoo J, Lin CT, Danoff S. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. Chest. 2018; 154: 1416-23.
16. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2016; 27: 1362.
17. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018; 4: 1721-8.
18. 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.
19. Nishino M, Hatabu H. Programmed death-1/programmed death ligand-1 inhibitor-related pneumonitis and radiographic patterns. J Clin Oncol. 2017; 35: 1628-9.
20. 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.
21. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. Chest. 2017; 152: 271-81.
22. De Velasco G, Je Y, Rosse D, Awad MM, Ott PA, Moreira RB, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. Cancer Immunol Res. 2017; 5: 312-8.
23. Naidoo J, Wang X, Woo KM, Irriborzh 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.
24. Lynch DA, Rose CS, Way D, King TE, Jr. Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol. 1992; 159: 669-72.
25. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29: iv264-iv66.
26. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018; 378: 158-68.
27. Suresh K, Naidoo J, Zhong Q, Xiong Y, Mammen J, de Flores MV, et al. The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis. J Clin Invest. 2019; 130: 4305-15.
28. Giancicchetti E, Fierabracci A. Inhibitory receptors and pathways of lymphocytes: the role of PD-1 in tumour development and their involvement in autoimmune onset and cancer progression. Front Immunol. 2018; 9: 2374.
29. Rowshanravan B, Halliday N, Sansom DM. CTLA-4: a moving target in immunotherapy. Blood. 2018; 131: 58-67.
30. Catarinco I, Scattone A, Silvestris N, Mangia A. Immune prophylaxis of lung cancer: the prognostic and predictive landscape of cellular and molecular immune markers. Transl Oncol. 2018; 11: 825-35.
31. Geng Y, Shao Y, He W, Hu W, Xu Y, Chen J, et al. Prognostic role of tumor-infiltrating lymphocytes in lung cancer: a meta-analysis. Cell Physiol Biochem. 2015; 37: 1560-71.
32. Zeng DQ, Yu YF, Ou QY, Li XY, Zhong RZ, Xie CM, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes for clinical therapeutic research in patients with non-small cell lung cancer. Oncotarget. 2016; 7: 13765-81.
33. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, et al. Profiling preexisting antibodies in patients treated with anti-PD-1 therapy for advanced non-small cell lung cancer. JAMA Oncol. 2019; 5: 376-83.
34. Naqash AR, Yang LV, Sanderlin EJ, Atwell DC, Walker PR. Interleukin-6 as one of the potential mediators of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint blockade: evidence from a case report. Acta Oncol. 2018; 57: 705-8.
35. Johnson DB, Balko JM. Biomarkers for immunotherapy toxicity: are cytokines the answer? Clin Cancer Res. 2019; 25: 1452-4.
36. Lim SY, Lee JH, Gide TN, Menzies AM, Guminiski A, Carlino MS, et al. Circulating cytokines predict immune-related toxicity in
melanoma patients receiving anti-PD-1-based immunotherapy. Clin Cancer Res. 2019; 25: 1557-63.

37. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Catravagl P. Piutzu expression of CTLA-4 mediates hypophitsis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014; 6: 230ra45.

38. Catravagl P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophitsis secondary to cytotoxic T-lymocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. Am J Pathol. 2016; 186: 3225-35.

39. Cui P, Liu Z, Wang G, Ma J, Qian Y, Zhang F, et al. Risk factors for pneumonitis in patients treated with anti-programmed death-1 therapy: a case-control study. Cancer Med. 2018; 7: 4115-20.

40. Sui J, Blumenthal GM, Jiand X, Ke K, Keegan P, Pazdur R. FDA approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. Oncologist. 2016; 21: 643-50.

41. Galant-Swafford J, Troesch A, Tran L, Weaver A, Doherty TA, Patel SP. Landscape of immune-related pneumonitis in cancer patients with asthma being treated with immune checkpoint blockade. Oncology. 2020: 98: 123-130.

42. Cho JY, Kim J, Lee JS, Kim YJ, Kim SH, Lee YJ, 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: 150-6.

43. Mark NM, Kargl J, Busch SE, Yang G, Metz HE, Zhang H, et al. Chronic obstructive pulmonary disease alters immune cell composition and immune checkpoint inhibitor efficacy in non-small cell lung cancer. Am J Respir Crit Care Med. 2018; 197: 325-36.

44. McKendry RT, Spalluto CM, Burke H, Nicholas B, Cellura D, Al-Shamkhani A, et al. Dysregulation of antiviral function of CD8(+) T cells in the chronic obstructive pulmonary disease lung. Role of the PD-1-PD-L1 axis. Am J Respir Crit Care Med. 2016; 193: 642-51.

45. 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.

46. Yamaguchi T, Shimizu J, Hasegawa T, Horio Y, Inaba Y, Yatabe Y, 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: 212-7.

47. Kato T, Masuda N, Nakanishi Y, Takahashi M, Hida T, Sakai H, et al. Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer. Lung Cancer. 2017; 104: 111-8.

48. Murashige N, Tanimoto T, Oshima Y. Interstitial lung disease and gefitinib. N Engl J Med. 2010; 363: 1578-9; author reply 79-80.

49. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001; 345: 638-46.

50. Lee LJ, Harris JR. Innovations in radiation therapy (RT) for breast cancer. Breast. 2009; 18(Suppl 3): S103-11.

51. Verellen D, De Ridder M, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. Nat Rev Cancer. 2007; 7: 949-60.

52. Herrera FG, Bourhis J, Couks G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. CA Cancer J Clin. 2017; 67: 65-85.

53. Levy A, Charchar C, Marabelle A, Perfetti NL, Magne N, Deutsch E. Can immunostimulatory agents enhance the abscopal effect of radiotherapy? Eur J Cancer. 2016; 62: 36-45.

54. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015; 372: 2018-28.

55. Shaverdian N, Lisberg AE, Bornayyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol. 2017; 18: 895-903.

56. Bradley JD, Nishio M, Okamoto I, Newton MD, Trani L, Shire NJ, et al. PACIFIC-2: phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC. J Clin Oncol. 2019; 37(15 Suppl): TP58573.

57. Lin SH, Lin Y, Mok I, Young IA, Phan S, Sandler A, et al. Phase II trial combining atezolizumab concurrently with chemoradiation therapy in locally advanced non-small cell lung cancer. J Clin Oncol. 2019; 37(15 Suppl): 8512.

58. Voong KR, Hazell SZ, Fu W, Hu C, Lin CT, Ding K, et al. Relationship between prior radiotherapy and checkpoint-inhibitor pneumonitis in patients with advanced non-small-cell lung cancer. Clin Lung Cancer. 2019; 20: e470-9.

59. von Reibnitz D, Chaft JE, Wu AJ, Samstein R, Hellmann MD, Plodkowski AJ, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition. Adv Radiat Oncol. 2018; 3: 391-8.

60. Owen DH, Wei L, Bertino EM, Edd T, Villalona-Calero MA, He K, et al. Incidence, risk factors, and effect on survival of immune-related adverse events in patients with non-small-cell lung cancer. Clin Lung Cancer. 2018; 19: e893-900.

61. Sekine I, Sumi M, Ito Y, Nokihara H, Yamamoto N, Kunitoh H, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. Radiother Oncol. 2006; 80: 93-7.

62. Chen Y, Williams J, Ding I, Hernady E, Liu W, Smudzin T, et al. Radiation pneumonitis and early circulatory cytokine markers. Semin Radiat Oncol. 2002; 12: 26-33.

63. 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.

64. Colen RR, Fujii T, Bilen MA, Kotrotsou A, Abrol S, Hess KR, et al. Radiomics to predict immunotherapy-induced pneumonitis: proof of concept. Invest New Drugs. 2018; 36: 601-7.
65. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018; 379: 2040-51.

66. Ahn MJ, Yang J, Yu H, Sakad H, Ramalingame S, Goto K, et al. 136O: osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: results from the TAILTON phase Ib trial. J Thor Oncol. 2016; 11: S115.

67. Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. JAMA Oncol. 2018; 4: 1112-15.

68. Schoenfeld AJ, Arbour KC, Rizvi H, Iqbal AN, Gadgeel SM, Girshman J, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. Ann Oncol. 2019; 30: 839-44.

69. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018; 378: 113-25.

70. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med. 2018; 378: 2093-104.

71. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, 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.

72. Ready N, Hellmann MD, Awad MM, Otterson GA, Gutierrez M, Gainor JF, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. J Clin Oncol. 2019; 37: 992-1000.

73. Yang JC, Gadgeel SM, Sequist LV, Wu CL, Papadimitrakopoulou VA, Su WC, et al. Pembrolizumab in combination with erlotinib or gefitinib as first-line therapy for advanced NSCLC with sensitizing EGFR mutation. J Thorac Oncol. 2019; 14: 53-59.

74. Chih-Hsin Yang J, Shepherd FA, Kim DW, Lee GW, Lee JS, Chang GC, et al. Osimertinib plus durvalumab versus osimertinib monotherapy in EGFR T790M-positive NSCLC following previous EGFR TKI therapy: CAURAL brief report. J Thorac Oncol. 2019; 14: 933-39.

75. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018; 378: 2078-92.

76. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med. 2018; 378: 2288-301.

77. Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SE, 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: 124-29.

78. Jotte RM CF, Vynnychenco I, Stroyakovskiy D, Abreu DR, Hussein MA, et al. IMpower131: primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + pembrolizumab vs carboplatin + paclitaxel or nab-paclitaxel vs. carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol. 2018; 36: 9000.

79. Voong KR HS, Hu C, Hayman J, Hales R, Marrone K, et al. MA 09.08 Receipt of chest radiation and immune-related pneumonitis in patients with NSCLC treated with anti-PD-1/PD-L1. J Thorac Oncol. 2017; 12: S1837.

80. 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: 1700050.

81. 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.

82. Shibiki R, Murakami S, Matsumoto Y, Yoshida T, Goto Y, Kanda S, et al. Association of immune-related pneumonitis with the presence of preexisting interstitial lung disease in patients with nonsmall lung cancer receiving anti-programmed cell death 1 antibody. Cancer Immunol Immunother. 2020; 69: 15-22.

83. National Comprehensive Cancer Network, Management Of ImmunoTherapy- Related Toxicities. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 14 Nov 2018.

84. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brissel KI, Cattelin 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.

85. Horvat T, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol. 2015; 33: 3193-8.

86. Andruska N, Mahapatra L, Hebbard C, Patel P, Paul V. Severe pneumonitis refractory to steroids following anti-PD-1 immunotherapy. BMJ Case Rep. 2018; 2018.

87. Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013; 144: 1419-25, 25 e1-3; quiz e19-20.

88. Ostor AJ, Chilvers ER, Somerville MJ, Lim AY, Lane SE, Crisp AJ, et al. Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. J Rheumatol. 2006; 33: 622-8.

89. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011; 41: 256-64.

90. Cheng R, Cooper A, Kench J, Watson G, Bye W, McNeil C, et al. Atezolizumab-induced toxicities and the gastroenterologist. J Gastroenterol Hepatol. 2015; 30: 657-66.

91. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kunze T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol. 2019; 20: e54-e64.
92. Jiang H, Gebhardt C, Umansky L, Beckhove P, Schulze TJ, Utikal J, et al. Elevated chronic inflammatory factors and myeloid-derived suppressor cells indicate poor prognosis in advanced melanoma patients. Int J Cancer. 2015; 136: 2352-60.

93. Liu W, Wang H, Bae F, Ding L, Huang Y, Lu C, et al. IL-6 promotes metastasis of non-small-cell lung cancer by up-regulating TIM-4 via NF-kappaB. Cell Prolif. 2020; 53: e12776.

94. von Itzstein MS, Khan S, Gerber DE. Investigational biomarkers for checkpoint inhibitor immune-related adverse event prediction and diagnosis. Clin Chem. 2020; 66: 779-93.

95. Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, et al. Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. J Dermatol Sci. 2017; 88: 225-31.

96. Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA. Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with PD-1 checkpoint inhibitors. Oncotarget. 2017; 8: 114268-80.

97. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol. 2018; 4: 374-8.

98. Ricciuti B, Genova C, De Giglio A, Bassanelli M, Dal Bello MG, Metro G, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. J Cancer Res Clin Oncol. 2019; 145: 479-85.

99. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, et al. Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab. Oncologist. 2018; 23: 1358-65.

100. Fukihrara J, Sakamoto K, Koyama J, Ito T, Iwano S, Morise M, et al. Prognostic impact and risk factors of immune-related pneumonitis in patients with non-small-cell lung cancer who received programmed death 1 inhibitors. Clin Lung Cancer. 2019; 20: 442-50 e4.

101. Suresh K, Peter KJ, Voong KR, Shankar B, Forde PM, Ettenger DS, et al. Impact of checkpoint inhibitor pneumonitis on survival in NSCLC patients receiving immune checkpoint immunotherapy. J Thorac Oncol. 2019; 14: 494-502.

102. Tone M, Izumo T, Awano N, Kuse N, Inomata M, Jo T, et al. High mortality and poor treatment efficacy of immune checkpoint inhibitors in patients with severe grade checkpoint inhibitor pneumonitis in non-small cell lung cancer. Thorac Cancer. 2019; 10: 2006-12.

103. Faiz SA, Balachandran DD, Bashoura L, Shannon VR. Pulmonary radiation recall induced by gemcitabine. Am J Respir Crit Care Med. 2016; 194: 909-10.

104. Azria D, Magne N, Zouhair A, Castadot P, Culine S, Ychou M, et al. Radiation recall: a well recognized but neglected phenomenon. Cancer Treat Rev. 2005; 31: 555-70.

105. Burris HA, 3rd Hurtig J. Radiation recall with anticancer agents. Oncologist. 2010; 15: 1227-37.

106. Chiang CL, Chen YW, Wu MH, Huang HC, Tsai CM, Chiu CH. Radiation recall pneumonitis induced by epidermal growth factor receptor-tyrosine kinase inhibitor in patients with advanced nonsmall-cell lung cancer. J Chin Med Assoc. 2016; 79: 248-55.

107. Ding X, Ji W, Li J, Zhang X, Wang L. Radiation recall pneumonitis induced by chemotherapy after thoracic radiotherapy for lung cancer. Radiat Oncol. 2011; 6: 24.

108. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of immune-related adverse events associated with immune checkpoint inhibitor therapy: a minireview of current clinical guidelines. Asia Pac J Oncol Nurs. 2019; 6: 154-60.

Cite this article as: Zhai X, Zhang J, Tian Y, Li J, Jing W, Guo H, et al. The mechanism and risk factors for immune checkpoint inhibitor pneumonitis in non-small cell lung cancer patients. Cancer Biol Med. 2020; 17: 599-611. doi: 10.20892/j.issn.2095-3941.2020.0102