

# Anti-PD-1/PD-L1 and anti-CTLA-4 associated checkpoint inhibitor pneumonitis in non-small cell lung cancer: Occurrence, pathogenesis and risk factors (Review)

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**Abstract.** Immune checkpoint inhibitors (ICIs) play a significant anti-tumor role in the management of non-small cell lung cancer. The most broadly used ICIs are anti-programmed death 1 (PD-1), anti-programmed cell death-ligand 1, and anti-cytotoxic T lymphocyte-associated antigen-4 monoclonal antibody. Compared with traditional chemotherapy, ICIs have the advantages of greater efficiency and more specific targeting. However, the resulting immune-related adverse events limit the clinical application of ICIs, especially checkpoint inhibitor pneumonitis (CIP). CIP chiefly occurs within 6 months of administration of ICIs. Excessive activation and

amplification of cytotoxic T lymphocytes, helper T cells, downregulation of regulatory T cells, and over-secretion of pro-inflammatory cytokines are the dominant mechanisms underlying the pathophysiology of CIP. The dysregulation of innate immune cells, such as an increase in inflammatory monocytes, dendritic cells, neutrophils and M1 polarization of macrophages, an increase in IL-10 and IL-35, and a decrease in eosinophils, may underlie CIP. Although contested, several factors may accelerate CIP, such as a history of previous respiratory disease, radiotherapy, chemotherapy, administration of epidermal growth factor receptor tyrosine kinase inhibitors, PD-1 blockers, first-line application of ICIs, and combined immunotherapy. Interestingly, first-line ICIs plus chemotherapy may reduce CIP. Steroid hormones remain the primary treatment strategy against grade  $\geq 2$  CIP, although cytokine blockers are promising therapeutic agents. Herein, the current research on CIP occurrence, clinical and radiological characteristics, pathogenesis, risk factors, and management is summarized to further expand our understanding, clarify the prognosis, and guide treatment.

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**Abbreviations:** ICI, immune checkpoint inhibitor; PD-1, programmed death 1; CIP, checkpoint inhibitor pneumonitis; RCT, randomized clinical trial; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; irAE, immune-related adverse event; OP, organizing pneumonia; NSIP, nonspecific interstitial pneumonia; HP, hypersensitive pneumonia; PFS, progression-free survival; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; TCR, T cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell; mAb, monoclonal antibody; PD-L2, programmed cell death-ligand 2; Th, helper T; Treg, regulatory T; CTL, cytotoxic T lymphocyte; IFN- $\gamma$ , interferon- $\gamma$ ; IL, Interleukin; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; BALF, bronchoalveolar lavage fluid; TIL, tumor-infiltrating lymphocyte; scRNA-seq, Single-cell RNA sequencing; DC, dendritic cell; OS, overall survival; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group

**Key words:** immune checkpoint inhibitors, checkpoint inhibitor pneumonitis, occurrence, pathogenesis, risk factors

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## 1. Introduction

According to the Global Cancer Statistics 2020 report, lung cancer ranks as the second most common type of cancer in incidence, accounting for 11.4% of all diagnosed cancer cases (1). Lung cancer is a prime contributor to cancer-related deaths, with 1.8 million global deaths from lung cancer each year (1). Non-small cell lung cancer (NSCLC) is the predominant

pathological type of lung cancer, accounting for ~85% of all reported cases (2). Patients with advanced NSCLC who received combination chemotherapy have a 5-year survival rate of only 2.8% (3).

Implementing immune checkpoint inhibitors (ICIs) can improve survival in advanced NSCLC. Pembrolizumab showed notable survival benefits in both previously untreated and treated advanced NSCLC, in which the 5-year survival rate was 23.2 and 15.5%, respectively (4). Programmed death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) blockers, including nivolumab, pembrolizumab, cemiplimab, atezolizumab, and durvalumab, have been authorized by the US Food and Drug Administration for advanced and metastatic NSCLC (5-7).

Additionally, anti-PD-1/PD-L1 treatments combined with anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) treatments have also been used for the management of advanced and recurrent NSCLC (8-11). The NEOSTER trial showed that the treatment with nivolumab combined with ipilimumab in neoadjuvant therapy for resectable NSCLC significantly increased the pathological response rate and reduced tumor retention (12).

The emergence of ICIs has revolutionized the therapeutic approaches for the management of NSCLC. Immune-related adverse events (irAEs) have also attracted significant attention, in particular, checkpoint inhibitor pneumonitis (CIP). CIP is more prone to occur in ICI-treated NSCLC than in other cancer types (13), with the rate of a grade  $\geq 3$  CIP being 2.3x higher than in different cancer types (14), which may be due to an increased chance of having respiratory comorbidities such as chronic obstructive pulmonary disease (COPD) and pre-existing interstitial lung disease (ILD) and receiving chest irradiation in NSCLC (13,15). Although CIP is rare, it has become one of the primary causes of ICI-related treatment interruption and death (16,17). The characteristics of occurrence, pathogenesis, high-risk factors, clinical and radiological manifestation, and management of CIP remain unclear; therefore, herein, the above issues are explored and summarized.

## 2. Occurrence of CIP

Among patients with malignant tumors who were administered PD-1/PD-L1 blockers, the global morbidity of irAEs was 26.82%, and the incidence of severe irAEs was 6.10% (6); common irAEs included pneumonia, colitis, hepatitis, rash, endocrine diseases, and nephritis (18). Following the Common Terminology Criteria for Adverse Events [version 5.0], CIP can be classified into 5 grades (19): In neoadjuvant therapy, anti-PD-1 therapy and combined immunotherapy had CIP rates of 1.1-5.0 and 5.0%, respectively; the occurrence of grade  $\geq 3$  CIP was 0.0-5.0% and 0.0, respectively (12,20,21). The incidence of CIP in first-line treatment with anti-PD-1/PD-L1 therapy and combined immunotherapy was 1.1-8.0 and 3.8-12.8%, respectively; the incidence of grade  $\geq 3$  CIP was 0-3.0 and 2.3-5.7%, respectively. In consolidation therapy, anti-PD-L1 therapy had CIP rates of 10.7-19.0%, and the incidence of grade  $\geq 3$  CIP was 1.7-3.0%. In second line and above treatment, anti-PD-1/PD-L1 therapy had CIP rates of 1.0-4.5%, and the incidence of grade  $\geq 3$  CIP was 0.0-2.1%

(Table I). However, a meta-analysis involving 1,885 patients with Stage III NSCLC showed that the incidence of CIP and the incidence of grade  $\geq 3$  CIP were 35 and 6%, respectively, when adopting durvalumab as a consolidation regimen in the real world (22). In retrospective studies, the incidence of CIP and the incidence of grade  $\geq 3$  CIP was 4.7-18.0 and 2.5-6.5%, respectively (Table II) (23-31). Based on the above studies, CIP in the real world is higher than that of prospective clinical trials.

Naidoo *et al* (6) retrospectively analyzed 915 patients who used PD-1/PD-L1 blockers, and found that the median time to CIP was 4.6 months (21 days to 19.2 months) in the ICI monotherapy group and the median time was 2.7 months (9 days to 6.9 months) in the combined therapy group. The time to CIP varies considerably in randomized clinical trials (RCTs). The CheckMate057 study showed that in 292 NSCLC patients who received nivolumab, the median time to CIP was 31.1 (11.7-56.9) weeks, while the CheckMate 017 trial showed a median time to CIP of 15.1 (2.6-85.1) weeks (32,33). The time to CIP in NSCLC adopting ICIs ranges from 39 days to 20 weeks in the real world (Table II). Suresh *et al* (34) divided CIP into early CIP (within 6 months after ICI) and late CIP (after 6 months of ICI). The results showed that CIP tended to occur early in NSCLC patients after initiating ICI treatment, with a higher CIP grade and higher early mortality. However, in the late CIP group, the grade of CIP was lower. In conclusion, CIP chiefly occurs within six months of ICIs. Since CIP is rare and has few cases, further large-sample trials are necessary to verify its law of occurrence.

## 3. Clinical and radiological characteristics

The typical clinical manifestations of CIP are dyspnea (38.5-78.6%), cough (22.7-88.1%), fever (9.1-40.5%), and chest pain (2.4-7.0%), although 8.8-33.0% of CIP patients are asymptomatic (6,35-40). Compared to other respiratory diseases, the clinical manifestations of CIP lack specificity. Therefore, radiological characteristics are critical to the diagnosis.

The prime radiological patterns of CIP are organizing pneumonia (OP) (65-86%), nonspecific interstitial pneumonia (NSIP) (15-31.3%), and hypersensitive pneumonia (HP) (7-38.1%). In addition, the unique radiological patterns of CIP include traction bronchiectasis, consolidation, reticular changes, central lobular nodules, and honeycomb changes (6,26,28,35,38,41,42). Studies have shown that the radiological characteristics of CIP are related to its severity. In grade  $\geq 3$  CIP, acute interstitial pneumonia (AIP) and acute respiratory distress syndrome (ARDS) are the primary manifestations, followed by OP, while in grade 1-2 CIP, NSIP, and HP are the most common manifestations (41). HP and cryptogenic organizing pneumonia were associated with improved efficacy of ICIs, with a median progression-free survival (PFS) of 44.29 weeks and 57 weeks, respectively (28). In addition, high-resolution computed tomography (HRCT) is promising for diagnosing CIP, especially when interstitial pulmonary fibrosis is considered (36). Clinical and radiological characteristics can help to establish a preliminary diagnosis of CIP, but tumor progression, infection, ILD, and thromboembolism must first be excluded (43).

Table I. CIP in NSCLC treated with ICIs in phase III randomized clinical trials.

A, Neoadjuvant 1st line treatment											
Trial, year of publication	Target	Treatment	NSCLC Stage	Histological type	Evaluable patients		Incidence of pulmonary toxicity, n (%)				(Refs.)
							Any-grade		Grade, ≥3		
					ICIs	Control	ICIs	Control	ICIs	Control	
Checkmate 816, 2022	PD-1	Nivolumab+Platinum	IB-III/A	NSCLC	176	176	2 (1.1)	1 (0.6)	0 (0.0)	1 (0.6)	(20)
KEYNOTE-024, 2016	PD-1	Pembrolizumab	IV	NSCLC	154	150	9 (5.8)	1 (0.7)	4 (2.6)	1 (0.7)	(134)
Checkmate 026, 2017	PD-1	Nivolumab	IV	NSCLC	267	263	3 (1.1)	1 (0.4)	3 (1.1)	0 (0.0)	(135)
CheckMate 227, 2018	PD-1	Nivolumab	IV	NSCLC	391	570	9 (2.3)	3 (0.5)	6 (1.5)	2 (0.4)	(9)
KEYNOTE-189, 2018	PD-1	Pembrolizumab+ Cisplatin/Carboplatin+ Pemetrexed	IV	Non-squamous	405	202	18 (4.4)	5 (2.5)	11 (2.7)	4 (2.0)	(136)
KEYNOTE-407, 2018	PD-1	Pembrolizumab+ Carboplatin+Paclitaxel/ Nab-paclitaxel	IV	Squamous	278	280	18 (6.5)	6 (2.1)	7 (2.5)	3 (1.1)	(137)
KEYNOTE-042, 2019	PD-1	Pembrolizumab	IIIB, IV	NSCLC	636	615	53 (8.0)	1 (0.2)	22 (3.0)	1 (0.2)	(138)
ORIENT-11, 2020	PD-1	Camrelizumab+ Platinum+ Pemetrexed	IV	Non-squamous	266	131	9 (3.4)	2 (1.5)	2 (0.8)	1 (0.8)	(139)
ORIENT-12, 2020	PD-1	Sintilimab+Platinum+ Gemcitabine	IV	Squamous	179	178	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	(140)
Camel, 2021	PD-1	Camrelizumab+ Carboplatin+ Pemetrexed	IV	Non-squamous	205	207	6 (3.0)	2 (<1.0)	4 (2.0)	1 (<1.0)	(141)
EMPOWER-Lung1, 2021	PD-1	Cemiplimab	IIIB-IV	NSCLC	355	342	5 (1.4)	12 (3.5)	4 (1.0)	7 (2.0)	(142)
IMpower150, 2018	PD-L1	Atezolizumab+ Bevacizumab+ Carboplatin+Paclitaxel	IV	Non-squamous	393	394	11 (2.8)	5 (1.3)	6 (1.5)	2 (0.5)	(143)
IMpower110, 2020	PD-L1	Atezolizumab	IV	NSCLC	286	263	21 (7.3)	27 (10.3)	7 (2.4)	10 (3.8)	(144)
MYSTIC, 2020	PD-L1	Durvalumab	IV	NSCLC	369	352	8 (2.2)	5 (1.4)	5 (1.4)	2 (0.6)	(11)
IMpower132, 2021	PD-L1	Atezolizumab+ Cisplatin/Carboplatin+ Pemetrexed	IV	Non-squamous	292	286	18 (6.2)	6 (2.2)	8 (2.1)	3 (1.1)	(145)
GEMSTONE-302, 2022	PD-L1	Sugemalimab+ Carboplatin+Paclitaxel/ Pemetrexed	IV	NSCLC	320	159	6 (2.0)	1 (1.0)	3 (1.0)	0 (0.0)	(146)

A, Neoadjuvant 1st line treatment

Trial, year of publication	Target	Treatment	NSCLC Stage	Histological type	Evaluable patients		Incidence of pulmonary toxicity, n (%)			
							Any-grade		Grade, ≥3	
					ICIs	Control	ICIs	Control	ICIs	Control
CheckMate 227, 2018	PD-1+ CTLA-4	Nivolumab+Ipilimumab	IV	NSCLC	576	570	22 (3.8)	3 (0.5)	13 (2.3)	2 (0.4)
	PD-1+ CTLA-4	Pembrolizumab+ Ipilimumab	IV	NSCLC	282	281	36 (12.8)	15 (5.3)	16 (5.7)	7 (2.5)
	PD-L1+ CTLA-4	Durvalumab+ Tremelimumab	IV	NSCLC	371	352	25 (6.7)	5 (1.4)	11 (3.0)	2 (0.6)
B, Consolidation										
Trial, year of publication	Target	Treatment	NSCLC Stage	Histological type	Evaluable patients		Incidence of pulmonary toxicity, n (%)			
							Any-grade		Grade, ≥3	
					ICIs	Control	ICIs	Control	ICIs	Control
PACIFIC, 2017	PD-L1	Durvalumab	III	NSCLC	475	234	51 (10.7)	16 (6.8)	8 (1.7)	6 (2.6)
	PD-L1	Sugemalimab	III	NSCLC	255	126	48 (19.0)	21 (17.0)	8 (3.0)	1 (<1.0)
C, 2nd line treatment										
Trial, year of publication	Target	Treatment	NSCLC Stage	Histological type	Evaluable patients		Incidence of pulmonary toxicity, n (%)			
							Any-grade		Grade, ≥3	
					ICIs	Control	ICIs	Control	ICIs	Control
CheckMate 017, 2015	PD-1	Nivolumab	IIIB, IV	Squamous	135	137	6 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)
	PD-1	Nivolumab	IIIB, IV	Non-squamous	292	290	8 (3.0)	1 (<1.0)	3 (1.0)	1 (<1.0)
Checkmate 010, 2016	PD-1	Pembrolizumab	IIIB, IV	NSCLC	682	309	31 (4.5)	6 (1.9)	14 (2.1)	2 (0.6)
	PD-1	Nivolumab	IV	NSCLC	337	156	15 (4.0)	0	4 (1.0)	0 (0.0)
CheckMate 078, 2019	PD-L1	Atezolizumab	IIIB, IV	NSCLC	609	578	6 (1.0)	1 (0.2)	4 (0.7)	0 (0.0)
OAK, 2017										
NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; Nab-paclitaxel, nanoparticle albumin-bound; CIP, checkpoint inhibitor pneumonitis.										

Table II. CIP in NSCLC treated with ICIs in retrospective studies.

First author, year	Histological type	Types of ICIs	Enrollment <sup>a</sup>	CIP, n (%)		Median time to onset of CIP (range)	(Refs.)
				Any-grade	Grade $\geq 3$		
Fukihara <i>et al</i> , 2019	NSCLC	PD-1 inhibitors	170	27 (16.0)	11 (6.5)	39 days (19-70 days)	(23)
Shibaki <i>et al</i> , 2020	NSCLC	PD-1 inhibitors	331	36 (11)	14 (4.2)	1.3 months (0.3-2.1 months)	(24)
Fujimoto <i>et al</i> , 2021	Non-squamous	PD-1 inhibitors	299	37 (12.4)	10 (3.3)	2.6 months (1.3-5.0 months)	(25)
Ono <i>et al</i> , 2021	NSCLC	PD-1 inhibitors	203	28 (14.0)	7 (3.4)	20 weeks	(26)
Chu <i>et al</i> , 2020	NSCLC	PD-1/PD-L1 inhibitors	300	54 (18.0)	8 (2.8)	3.8 months (0.7-21.0 months)	(27)
Cui <i>et al</i> , 2020	NSCLC	PD-1/PD-L1 inhibitors	276	42 (15.2)	7 (2.5)	134 days (20-687 days)	(28)
Huang <i>et al</i> , 2021	NSCLC	PD-1/PD-L1 inhibitors	677	32 (4.7)	22 (3.2)	10 weeks (0.1-71 weeks)	(29)
Yamagata <i>et al</i> , 2021	NSCLC	PD-1/PD-L1 inhibitors	222	27 (12.2)	7 (3.2)	1.9 months (0.9-6.1 months)	(30)
Chao <i>et al</i> , 2022	NSCLC	PD-1/PD-L1 inhibitors	164	20 (12.2)	7 (4.3)	2.9 months (13 days-19.2 months)	(31)

<sup>a</sup>Enrollment, patients receiving ICIs. ICI, immune checkpoint inhibitor; CIP, checkpoint inhibitor pneumonitis.

#### 4. Pathogenesis of CIP

*Mechanism of action of CTLA-4, PD-1, and PD-L1 monoclonal antibody (mAb).* Tumor cells typically use immune suppression and tolerance mechanisms to evade immune clearance, activating CTLA-4 and PD-1/PD-L1 signals to destroy or inhibit immune regulatory pathways (44). CTLA-4 is structurally similar and homologous to the T cell co-stimulatory molecule Cluster of Differentiation 28 (CD28). CTLA-4 can compete with CD28 to bind to the ligands B7-1 (CD80) and B7-2 (CD86). CTLA-4 has greater affinity and activity than CD28, reducing CD28/B7 interactions, and may transmit intracellular inhibitory signals after binding to B7 molecules (45). In addition, studies have confirmed that CTLA-4 can remove CD80 and CD86 molecules on the surface of antigen-presenting cells (APCs), which reduces the activation of effector T cells (46).

PD-L1 is one of the ligands of PD-1 and is primarily expressed on somatic cells exposed to anti-inflammatory cytokines. The binding of PD-1 and PD-L1 inhibits the effects of T cells (44,47). At the same time, chronic inflammatory factor-mediated expression of PD-L1 in the tumor microenvironment leads to PD-1-mediated depletion of T cells and inhibits the anti-tumor cytotoxic T cell response (47-49). That is, the binding between CTLA-4 and B7 molecules, removing B7 molecules from APCs, and the relationship between PD-1 and PD-L1 ultimately reduces the activation of T cells, thus improving the survival of tumor cells. This mechanism suggests that CTLA-4 mAbs can block CTLA-4 inhibitory signals, and PD-1 and PD-L1 mAbs can block PD-1/PD-L1 inhibitory signals, restoring T cells' tumor-killing effect and achieving tumor growth inhibition (Fig. 1) (43).

Anti-PD-1, anti-PD-L1, and anti-CTLA-4 mAb can block CTLA-4 and PD-1/PD-L1 signaling, respectively. This process may also lead to excessive activation and amplification of CTL, Helper T (Th) cells, and downregulation of regulatory T cells (Tregs), and ultimately lead to induction of CIP (Fig. 2) (50-52).

*Cytotoxic T lymphocyte (CTL).* Prior to treatment with steroids, analysis of bronchoalveolar lavage fluid (BALF) from 12 CIP patients and 6 patients without CIP showed that the number of lymphocytes increased by >20% in the CIP group. Subsequent flow cytometry analysis revealed that the CD3<sup>+</sup>CD8<sup>+</sup>T cells and TNF- $\alpha$ <sup>high</sup>IFN- $\gamma$ <sup>high</sup> CD8<sup>+</sup>T cells increased (50). Histochemical analysis of pneumonia tissues from CIP patients revealed that CD8<sup>+</sup>T cells increased in pneumonia tissues (51). During steroid reduction, the specific proliferation of PD-1<sup>+</sup>CD8<sup>+</sup> T cells was observed in the pulmonary pathology of relapsed CIP but not in normal tissues (53).

Furthermore, comparison of the complementarity-determining region 3 of the T cell receptor (TCR)  $\beta$  chain in irAE-lesions and tumor-infiltrating lymphocytes (TILs) via sequencing revealed that the T cell pools of two groups overlapped significantly (51). Subudhi *et al* (54) found that the number of CD8<sup>+</sup>T cell clones in the peripheral blood was closely correlated with irAEs (P=0.01), especially with grade 2-3 irAEs (P<0.0001) in patients who received ipilimumab, a CTLA-4 blocker. TIL-like T cells in inflammatory tissues and peripheral blood suggest the existence of cross-antigens shared

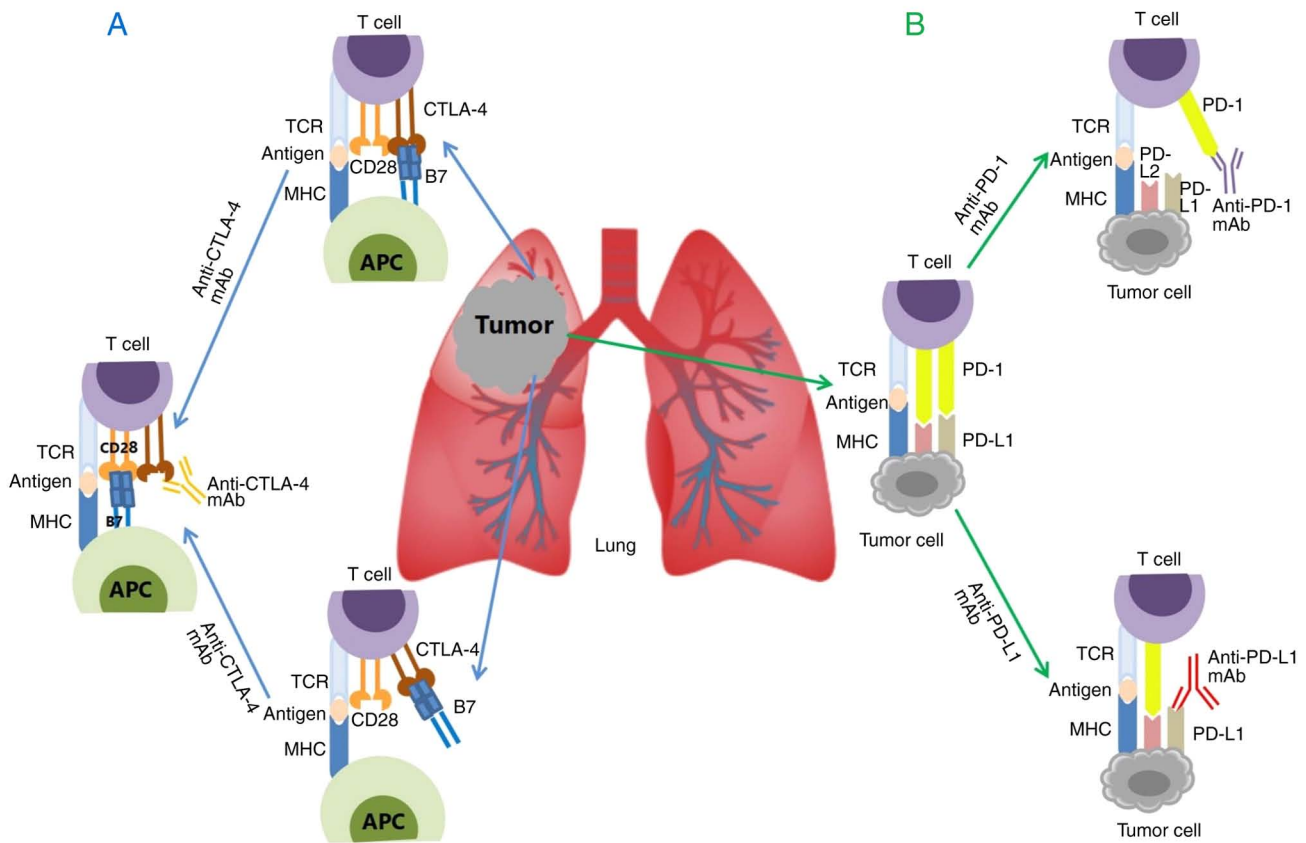


Figure 1. Mechanism of action of anti-CTLA-4, anti-PD-1, and anti-PD-L1 mAbs. (A) Mechanism of action of anti-CTLA-4 mAb (blue arrow). (B) Mechanism of action of anti-PD-1 and anti-PD-L1 mAbs (green arrow). TCR, T cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; mAb, monoclonal antibody.

in tumor and normal tissues. If the cross-antigens appeared in the lung tissue, the specific CTL may damage the normal lung tissue and thereby cause CIP.

**Th cells.** A previous study showed that CD3<sup>+</sup>CD4<sup>+</sup> cells in the BALF were elevated in CIP compared with the control group ( $P=0.04$ ). The differential clustering map of T-cell subsets suggested that CD4<sup>+</sup>FoxP3<sup>lo</sup>CD25<sup>+</sup>CD62L<sup>hi</sup>CD45RA<sup>lo</sup> clusters were markedly increased in the CIP group (50). Naive CD4<sup>+</sup> T cells can differentiate into Th1, Th2, and Th17 subsets under the stimulation of cytokines such as IL-6, TGF- $\beta$ , and IFN- $\gamma$  (55). In the following sections, the impact of CD4<sup>+</sup> T cell subsets in the development of CIP is summarized.

**Th1 cells.** Th1 cells can secrete IFN- $\gamma$  and play a vital anti-cancer role by activating CTL (56). The proportion of Th1 cells reportedly decreased in the NSCLC immunological background (57). PD-1 blockers can enhance Th1 and Th17 effector cytokines, such as IL-2, IFN- $\gamma$ , TNF $\alpha$ , IL-6, and IL-17, transforming antigen-induced cell reactivity into a proinflammatory Th1/Th17 response (58). Th1 cells play a dominant role in Nivolumab-mediated irAEs (59). In a previous study, the analysis of T-cell subsets in BALF of the CIP group ( $n=13$ ) indicated that the percentages of Th1 cells were higher when CIP occurred compared with the baseline ( $P=0.029$ ). The Th1/Th2 ratio decreased when the severity of CIP was reduced ( $P=0.042$ ) (60). The enrichment of Th1 cells was also

observed in BALF of leukemia patients with CIP treated with ICIs (39). Therefore, the dominance of Th1 cells may be one of the mechanisms leading to CIP.

**Th17.** IL-6 and TGF can activate the transformation of naive CD4<sup>+</sup> T cells into Th17 cells (56). Th17 cells primarily consist of the anatomical barrier structures of the digestive tract and lung and produce IL-17 (61). Th17 cells in the lungs can recruit and cause significant activation of tumor-specific CD8<sup>+</sup> T cells (62). In NSCLC, the analysis of T cell subsets in BALF of the CIP patients indicated that the percentage of Th17 cells and the ratio of Th17 to Tregs was higher when CIP occurred compared with the baseline ( $P=0.014$  and  $P=0.002$ , respectively) (60). The proportion of CD4<sup>+</sup> T<sub>H17.1</sub> cells in the CIP group was significantly higher than those in the control group (13 vs. 3%) via single-cell RNA sequencing (scRNA-seq) analyses, especially the pathogenic T<sub>H17.1</sub>TB<sub>X21</sub> cells. Subsequent T-cell receptor sequencing revealed that the Gini coefficient increased and TCR abundance and evenness decreased in T<sub>H17.1</sub>TB<sub>X21</sub> cells, which further suggested that T<sub>H17.1</sub>TB<sub>X21</sub> cells had an apparent ability of antigen-driven clonal expansion (63). Thus, Th17 cells can promote CIP by activating CD8<sup>+</sup> T cells and participate in CIP directly through antigen-mediated specific proliferation.

**Tregs.** Tregs belong to the inhibitory CD4<sup>+</sup> T cell subgroup, which is primarily involved in establishing peripheral tolerance by inhibiting effector T cells and inhibiting immune-mediated



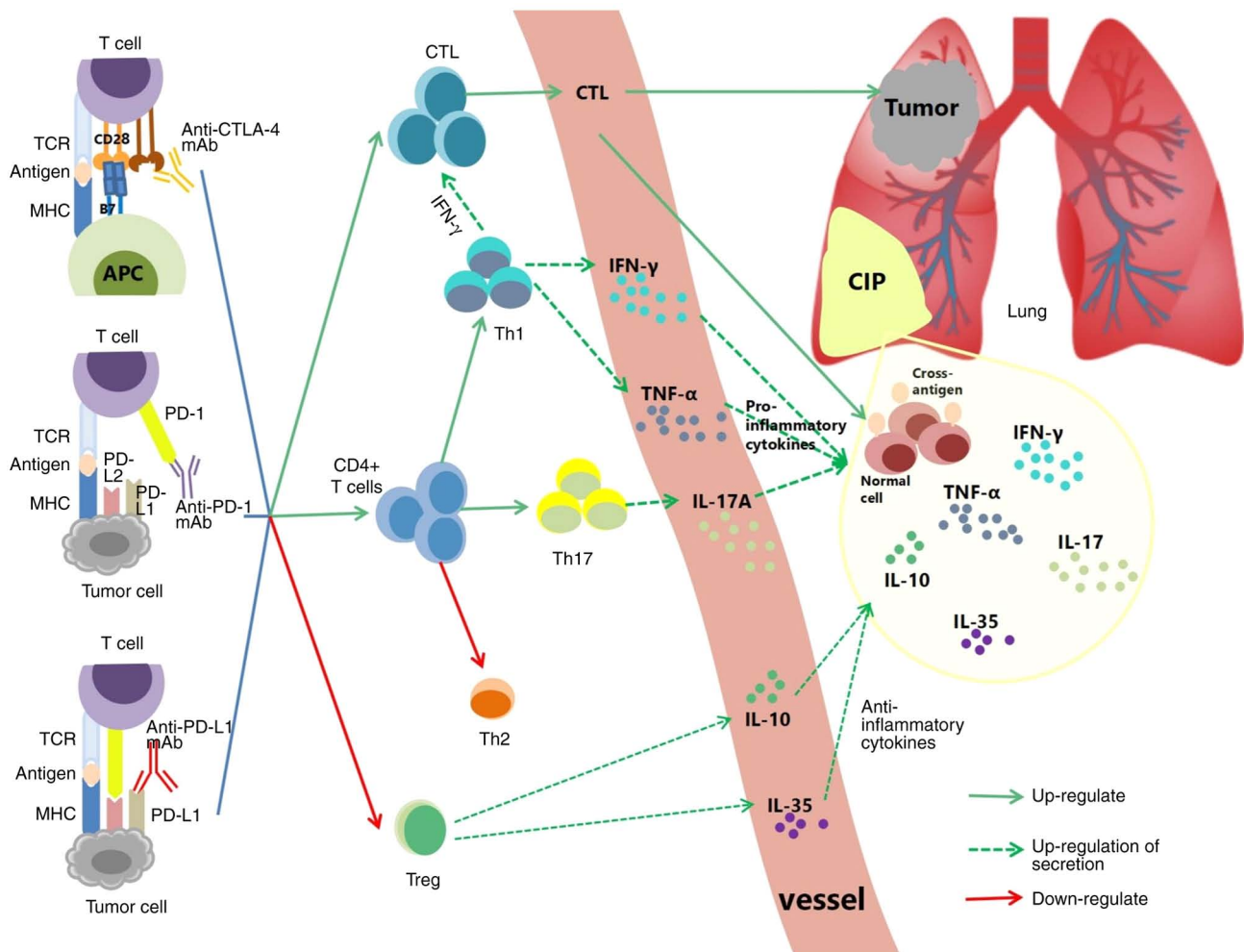


Figure 2. Mechanisms of action of T cells and correlative cytokines in CIP. Anti-PD-1, anti-PD-L1, and anti-CTLA-4 mAbs can block CTLA-4 and PD-1/PD-L1 signaling, enhancing the activation and proliferation of CD4+T cells and CTL and weakening the inhibitory effect of Tregs. CTL kills not only tumor cells but also normal lung tissues that express the same antigens as tumor cells. Th2 cells differentiated from CD4+T cells are downregulated, while Th1 and Th17 cells are upregulated in this process and secrete more IFN- $\gamma$ , TNF $\alpha$ , and IL-17A into the peripheral blood. IFN- $\gamma$  can promote the amplification of CTL. Meanwhile, IL-10 and IL-35, secreted by Tregs, are secondarily elevated due to the pro-inflammatory response. Then cytokines reach the lung through blood circulation. The above-dysregulated secretion of cytokines and immune cell-killing mechanisms jointly promote CIP. CTL, cytotoxic T lymphocyte; Treg, regulatory T; CIP, checkpoint inhibitor pneumonitis; Th, helper T; IFN- $\gamma$ , Interferon- $\gamma$ ; IL, interleukin; TNF $\alpha$ , tumor necrosis factor  $\alpha$ ; CTLA-4, CTL-associated antigen-4; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; mAb, monoclonal antibody; TCR, T cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell.

tissue destruction against autoantigens. PD-1<sup>+</sup> and CTLA-4<sup>+</sup> Tregs negatively regulate the inflammatory response induced by CD8<sup>+</sup>T cells (52,64). Since the PD-1/PD-L1 axis is blocked, Treg differentiation is blocked, leading to a decrease in Treg levels in the tumor microenvironment (38). The conjugation of anti-CTLA-4 antibodies to CTLA-4 can also lead to Treg depletion or functional blockade, thereby enhancing T-cell activation (52). The proportion of immunosuppressive CTLA-4<sup>high</sup>PD-1<sup>high</sup> alveolar Tregs is notably decreased in the BALF following the development of CIP (50), which may promote Th1 cell responses, as seen in NSCLC patients with CIP (60). Not only does Treg depletion facilitate CIP, but alveolar Tregs participate in the regression of lung injury (65). Thus, the depletion and dysfunction of Tregs may accelerate CIP.

**Innate immune cells.** In addition to T cells, innate immune cells may be vital for CIP (Fig. 3). A prospective study that consisted of 11 CIP patients found marked monocyte/macrophage

depletion in the BALF of patients with CIP, but a substantial elevation of dendritic cells (DCs). Further scRNA-seq analysis revealed that the proportion of pro-inflammatory *IL-1B<sup>high</sup>* monocytes was increased, and 'M1-like' genes such as *CCL3*, *CCL4*, *IL1B*, *TNF*, and *NFKB1A* were up-regulated in monocytes/macrophages in CIP (63). Upregulation of M1-type macrophages was also observed in NSCLC patients who developed CIP (66). Recent studies have demonstrated that eosinophils may be involved in CIP. By analyzing the peripheral blood of 430 lung cancer patients treated with ICIs, Li *et al* (67) observed that eosinophils in the CIP group (n=67) differed at the beginning of ICI treatment ( $E_{bas}$ ), diagnosis of CIP ( $E_{end}$ ), and 1 week after CIP diagnosis ( $E_{fol}$ ). The  $E_{end}/E_{bas}$  ratio signally decreased and was correlated with the severity of CIP. The risk and severity of CIP were incremental when  $E_{end}/E_{bas} < 0.5$ .  $E_{fol}$  notably rose, and the CIP patients had a prolonged overall survival (OS) when  $E_{fol}/E_{bas} \geq 1.0$  (20.9 vs. 8.2 months,  $P=0.024$ ). A positive

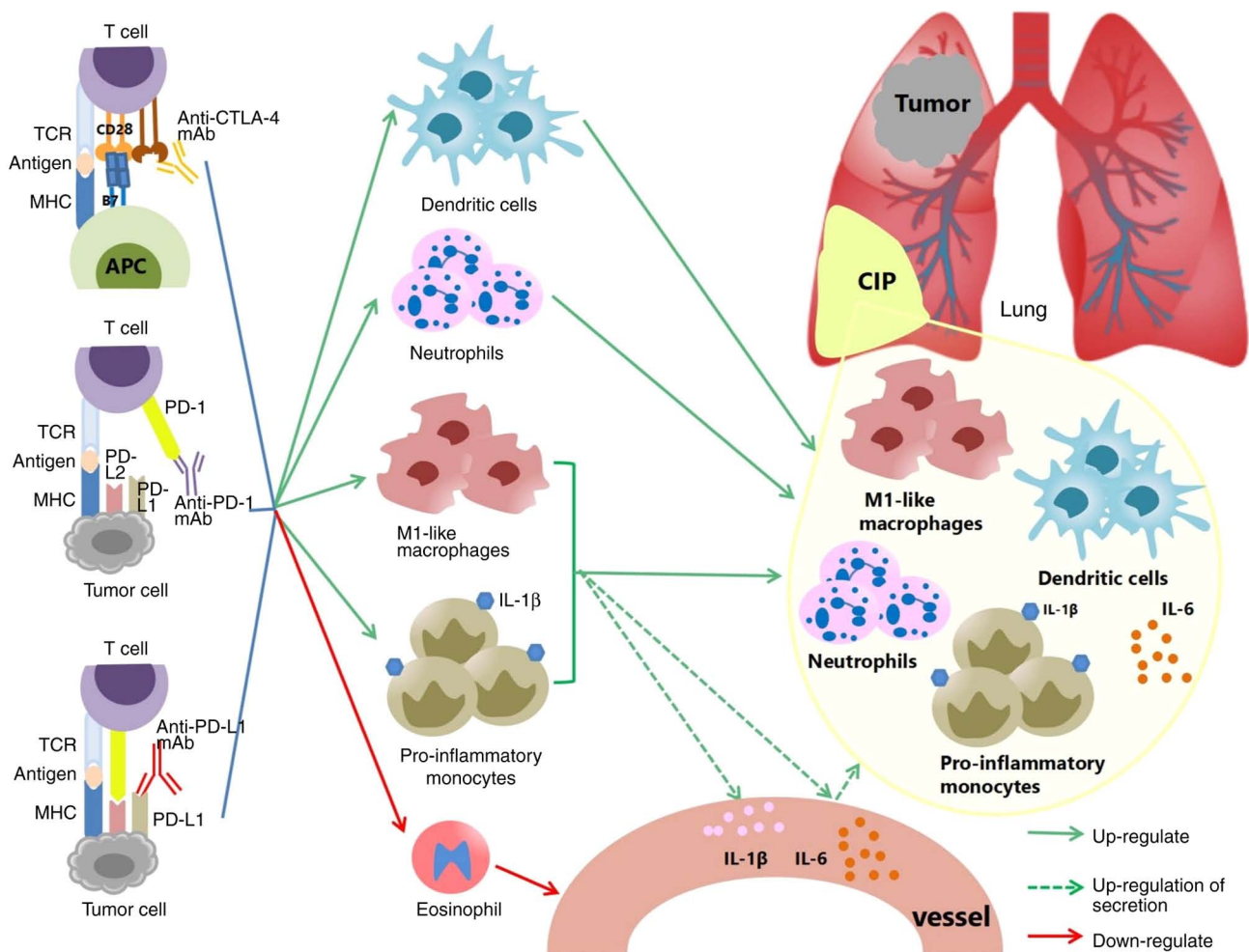


Figure 3. Mechanisms of action of innate immune cells and correlative cytokines in CIP. Blockade of CTLA-4 and PD-1/PD-L1 signaling by anti-PD-1, anti-PD-L1, and anti-CTLA-4 mAbs resulted in the reduction of eosinophil and the elevation in IL-6 and IL-1β secreted by monocytes and macrophages in peripheral blood. Meanwhile, the increase of pro-inflammatory M1-like macrophages, monocytes expressing IL-1β, dendritic cells, neutrophils, and IL-6 were observed in CIP. The dysregulation of innate immune cells and increase in pro-inflammatory cytokines promoted CIP. CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death 1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; mAb, monoclonal antibody; TCR, T cell receptor; MHC, major histocompatibility complex; IL, interleukin; APC, antigen-presenting cell; CIP, checkpoint inhibitor pneumonitis.

association between high baseline eosinophil levels and CIP was also observed in NSCLC, and the high eosinophil group (eosinophils  $\geq 0.125 \times 10^9$  cells/l) had a superior PFS compared with the low-eosinophil group (eosinophils  $< 0.125 \times 10^9$  cells/l) (8.93 vs. 5.87 months,  $P=0.038$ ) (27). In addition, elevated neutrophil counts and infiltration were observed in the BALF and pathological tissues of the inflammatory sites in CIP patients, respectively (68,69). These findings suggest that the increase in inflammatory monocytes, DCs, and neutrophils, M1 polarization of macrophages, and decrease in eosinophils may influence the occurrence and development of CIP.

**Cytokines.** In addition to immune cells, cytokines are also involved in the development of CIP. The dysregulation of cytokines is associated with severe irAEs and may thus be used in determining a prognosis (70).

**IL-6.** IL-6 is an essential cytokine in the acute phase of inflammation (71), with pro-inflammatory effects in the tumor microenvironment (72). IL-6 inhibits Treg development and promotes the production of effector Th17 cells (73).

Lin *et al* (74) found that IL-6 levels in the peripheral blood were elevated at the onset of CIP (11.81 vs. 7.62 pg/ml). The OS in the IL-6  $< 11.81$  pg/ml group and  $\geq 11.8$  pg/ml group was 21.1 and 6.1 months ( $P<0.001$ ), respectively, demonstrating that high levels of IL-6 may facilitate CIP and shorten survival. IL-6 levels are markedly different between the acute and chronic phases of CIP (17.9 vs. 5.7 pg/ml,  $P=0.018$ ) (75). Analysis of the cytokines in the BALF also indicated that IL-6 was significantly higher in the CIP group than that in the lung cancer group [126.0 pg/ml (14.6–248.9 pg/ml) vs. 1.5 pg/ml (0.7–7.8 pg/ml),  $P=0.011$ ] (68). Thus, elevated levels of IL-6 are not only involved in CIP, but it also has a predictive effect on the prognosis.

**IL-17A.** IL-17A produced by Th17 cells, is a pro-inflammatory cytokine involved in various inflammatory diseases. Overexpression of IL-17A and Th17 cells leads to tissue damage, inflammation, and autoimmune activation (76–78). Spleen cells of PD-1<sup>-/-</sup> mice have been reported to produce more IL-17A than wild-type mice post-stimulation (concanavalin A, PMA + Ionomycin, or  $\alpha$ CD3 +  $\alpha$ CD28) (79). High levels of IL-17 at baseline were predictive of grade 3 diarrhea/enteritis



in melanoma treated with ipilimumab ( $P=0.02$ ) (80). IL-17A levels in the serum and BALF were elevated when CIP occurred in NSCLC patients. IL-17A in serum significantly decreased when CIP was improved or restored ( $P=0.034$ ) and was positively correlated with the proportion of Th17 cells and the Th17/Treg ratio (60). Another study demonstrated that IL-17A in the BALF of CIP patients was significantly higher than that of lung cancer and ILD patients (68). In conclusion, elevated IL-17A levels may promote CIP.

**IL-1 $\beta$ .** IL-1 $\beta$  is a critical pro-inflammatory factor, primarily synthesized and secreted by monocytes and macrophages. High levels of IL-1 $\beta$  in the serum can promote acute lung injury and pulmonary fibrosis (67,81). Elevated IL-1 $\beta$  at baseline and early in anti-PD-1 therapy (1-6 weeks after anti-PD-1 therapy) is predictive of irAEs (70). A case report demonstrated that the levels of IL-1 $\beta$  were significantly elevated in the serum of CIP patients (21.9 pg/ml) (82). Suresh *et al* (50) observed that the number of monocytes expressing IL-1 $\beta$  in the BALF increased noticeably, while soluble IL-1 $\beta$  levels decreased during the development of CIP. This may be due to the late time of BALF collection (at least 2-3 days after the onset of CIP symptoms), whereas elevations in IL-1 $\beta$  generally occur early in lung injury. According to the above studies, IL-1 $\beta$  may be involved in the pathogenesis of CIP through pro-inflammatory responses, although its secretion in CIP requires further observation and analysis.

**IL-10 and IL-35.** IL-10 and IL-35, which are produced by Tregs, are important anti-inflammatory cytokines with anti-fibrotic effects (83,84). IL-10 can inhibit the production of TNF- $\alpha$ , IL-6, and IL-1 $\beta$  of monocytes (85). IL-35 can reduce the activation of Th1 and Th17 cells and inhibit the secretion of cytokines such as IL-17A, TNF- $\alpha$ , and IFN- $\gamma$  (86,87). IL-35 can promote the production of IL-10 (88). IL-10 is elevated when CIP occurs, and high levels of IL-10 ( $\geq 3.79$  pg/ml) are positively correlated with severe CIP ( $P=0.057$ ) (74). Wang *et al* (89) performed a subgroup analysis of 40 NSCLC patients with irAEs and found baseline IL-10 levels were an independent prognostic risk factor for CIP (OR=9.969, 95% CI 1.144-86.843,  $P=0.037$ ). CIP was prone to occur in the high IL-10 group ( $\geq 0.704$  pg/ml) compared with the low IL-10 group ( $< 0.704$  pg/ml) (45.65 vs. 9.52%,  $P=0.004$ ). The levels of IL-35 in the serum and BALF were elevated when CIP occurred in NSCLC patients. IL-35 levels in the serum were significantly decreased when CIP improved or resolved ( $P=0.044$ ) and positively associated with the proportion of Th1 cells and the Th1/Th2 ratio (60). In conclusion, IL-10 and IL-35 may influence CIP, while an increase in the levels of IL-10 and IL-35 may be secondary to the pro-inflammatory response. However, the specific mechanism warrants further exploration.

**Other potential mechanisms.** In addition to the aforementioned immune disorders and abnormal cytokine secretion, autoantibodies, and microbial flora may also affect the occurrence of CIP. In NSCLC patients who were treated with PD-1 blockers, irAEs were found to be associated with preexisting rheumatoid factor (68 vs. 40%,  $P=0.006$ ) and autoantibodies (60 vs. 32%,  $P=0.002$ ), such as thyroid peroxidase antibody, anti-thyroglobulin, and antinuclear antibody; however, no statistical differences in the occurrence of CIP was found in the subgroup analyses (90).

Tumor-associated autoantibodies can increase CIP, such as antibodies against p53, NY-ESO-1, TRIM21, HUD, and BRCA2 (91). Furthermore, the levels of anti-CD74 autoantibodies increased 1.34-fold in patients with CIP compared with before treatment with ICIs, but the fold increase was not observed in patients without CIP, which revealed that the fold-change of anti-CD74 autoantibodies was related to the development of CIP (92). The relationship between microbial flora and irAEs has also attracted attention. For example, the enrichment of *Firmicutes* is more likely to lead to ICI-related diarrhea (93). However, the connection between CIP and microbial flora is vague.

## 5. Risk factors for CIP

**Previous respiratory disease.** In real-world settings, several NSCLC patients have pre-existing respiratory diseases, such as ILD, COPD, and asthma. Pre-existing ILD may accelerate CIP in NSCLC (35,38,94-96), and CIP was found to occur earlier in NSCLC patients with previous ILD during ICI treatment (1.3 vs. 2.3 months) (24). In another study consisting of 461 NSCLC patients, the ILD group ( $n=49$ ) more frequently developed CIP ( $n=412$ ) (30.6 vs. 9.5%,  $P<0.01$ ) and grade  $\geq 3$  CIP (16.3 vs. 3.6%,  $P<0.01$ ) than the non-ILD group (97). However, mild ILD may not increase the incidence of CIP and grade  $\geq 3$  CIP. Fujimoto *et al* (98) defined mild interstitial pneumonia as a predicted vital capacity of  $\geq 80\%$  and manifesting as usual interstitial pneumonia on HRCT. In their study, CIP occurred in only 2 of 18 NSCLC patients after nivolumab therapy, both grade 2. In another study involving 10 patients with mild ILD, it was also found that there was no significant difference in the incidence and severity of CIP between those with and without prior ILD who received first-line pembrolizumab monotherapy in NSCLC (20.0 vs. 22.6% and 10.0 vs. 11.3%, respectively) (99).

In conclusion, the application of PD-1 blockers in patients with mild ILD may be safe, but more severe ILD may be more closely related to CIP in NSCLC, which requires further confirmation. Interestingly, adopting the anti-PD-L1 mAb in a bleomycin-induced pulmonary fibrosis mouse model can alleviate pulmonary fibrosis (100). There is substantial heterogeneity in the effects of PD-L1 blockers in ILD. Further comparison and analysis of the immune background of patients with ILD who develop CIP and the changes in the microenvironment during the development of the two diseases are necessary, which may offer a reliable basis for utilizing ICIs in NSCLC with pre-existing ILD. In addition, COPD and asthma may also contribute to CIP (101,102). In the KEYNOTE-001 trial, CIP was more common in patients with prior COPD and asthma (5.4 vs. 3.1%) (101). Grades 3-4 CIP was more prone to occur in patients with concomitant asthma (100.0 vs. 28.6%) (103).

**Previous/combined/sequential radiotherapy, chemotherapy, and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).** Radiotherapy may be a risk factor for CIP (104-106). NSCLC patients with a history of chest radiotherapy are more prone to CIP than patients without a history of chest radiotherapy (40 vs. 9.8%,  $P<0.001$ ), and grade  $\geq 3$  CIP occurred in 10% of patients, all of which had a history of

chest radiotherapy (104). CIP was independent of parameters of previous radiotherapy, but patients who received curative-intent chest radiotherapy (definitive, adjuvant, or consolidative radiation) were more likely to develop CIP in the subgroup analyses (89 vs. 11%) (107). A pronounced increase in pulmonary toxicity among patients with a history of previous thoracic and dorsal radiotherapy (13 vs. 1%,  $P=0.046$ ) was also discovered in the KEYNOTE-001 trial. Interestingly, patients who received chest radiotherapy before pembrolizumab administration showed a more substantial survival benefit (106). A meta-analysis including 9,500 NSCLC patients demonstrated that CIP was more likely to occur with ICI plus chemotherapy than with ICI alone (6.03 vs. 3.32%,  $P=0.01$ ) (108). Another meta-analysis of RCTs showed that the incidence of CIP and grade  $\geq 3$  CIP in first-line treatment of NSCLC was lower in the ICI plus chemotherapy group than in the ICI monotherapy group (5.9 vs. 7.1% and 1.6 vs. 2.9%, respectively) (109). Matsuo *et al* (110) also demonstrated that CIP in the first-line treatment of NSCLC was higher in ICI monotherapy ( $n=172$ ) than that in the ICI plus chemotherapy ( $n=38$ ;  $P=0.029$ ). Moreover, CIP in patients treated with EGFR-TKIs plus nivolumab was four times higher than that of nivolumab monotherapy (111). In the TATTON trial, osimertinib plus durvalumab was discontinued due to the increased reporting of ILD (22%) (112).

**Types of ICIs.** A meta-analysis found that compared with PD-L1 blockers, the use of PD-1 blockers was more likely to result in a patient developing CIP, with Grade 3 or 4 pneumonitis also being more commonly observed with PD-1 blockers (1.1 vs. 0.4%,  $P=0.02$ ) (108,113). A higher incidence of grade  $\geq 3$  CIP was also observed in patients treated with PD-1 blockers compared with PD-L1 blockers in stage III NSCLC (8.6 vs. 4.4%,  $P=0.01$ ) (114). A review involving 48 trials demonstrated that CIP was more likely to occur with PD-1 blockers than CTLA-4 blockers (OR 6.4, 95% CI 3.2-12.7) (115). CIP was more common when treated with pembrolizumab than with nivolumab (63 vs. 37%,  $P=0.004$ ) (23). Additionally, untreated NSCLC is more likely to result in CIP compared with NSCLC previously treated with PD-1/PD-L1 blockers (113). Compared with the use of ICIs as a second-line treatment, CIP and grade  $\geq 3$  CIP were more likely to occur if ICIs were used as a first-line treatment (14,108). The KEYNOTE-598 trial showed that pembrolizumab plus ipilimumab was more likely to result in CIP and grade  $\geq 3$  CIP than pembrolizumab alone (12.8 vs. 5.3% and 5.7 vs. 2.5%, respectively) (10). In the Lung-MAP S1400I trial (8) and the MYSTIC trial (11), the morbidity of CIP and grade  $\geq 3$  CIP in the PD-1/PD-L1 plus CTLA-4 blocker group tended to be higher compared with that in the PD-1/PD-L1 blocker monotherapy group.

**Other risk factors.** Excluding previous respiratory disease, the history of radiotherapy, chemotherapy, and EGFR-TKI therapy, and types of ICIs, age (35,116), smoking history (117,118), histological type (34,117), Eastern Cooperative Oncology Group (ECOG) score (38,42), extra-thoracic metastasis (35,119), serum albumin (23), and lung function (120) may be related to the occurrence of CIP.

However, several studies have shown that age, sex, smoking history, ECOG score, extra-thoracic metastasis, histological type, previous COPD, previous chemotherapy, radiotherapy,

and EGFR-TKI treatment history, and the type of ICIs are not related to the occurrence of CIP (28,35,43,50,116).

## 6. Management and prognosis of CIP

According to the guidelines and consensus recommendations for grade 1 CIP, monitoring symptoms and pulmonary function, and performing a chest CT is recommended. If symptoms improve, close follow-up and ICI treatment should be resumed. However, if conditions worsen, ICI treatment should be suspended. For grade 2 CIP, ICI should be suspended, and methylprednisolone 1-2 mg/kg/d should be administered intravenously. After 48-72 h of treatment, if the symptoms improve, the steroid dose should be reduced by 5-10 mg per week for 4-6 weeks. If the disease worsens, the treatment plan should be escalated. If there is the possibility of a co-infection, empirical and spectral antibiotic therapy should be considered. Chest CT and pulmonary function should be reviewed every 3-4 days. When the patient recovers to grade  $\leq 1$  CIP, the resumption of immunotherapy should be considered. For grade 3-4 CIP, ICIs should be discontinued permanently, the patient should be hospitalized, and methylprednisolone 2-4 mg/kg/d should be administered intravenously after 48 h of treatment. If the symptoms improve, the dose of the steroid should be reduced after 8 weeks of treatment. If the symptoms worsen, other immunosuppressants should be considered (121-123).

There are currently four RCTs exploring CIP treatment on the National Institutes of Health ongoing Trial Registry, of which NCT04438382, NCT05899725, and NCT05280873 are recruiting patients, and NCT04036721 was suspended due to SARS-CoV-2 cases. Therefore, the outcomes of treatment for CIP in randomized clinical trials are currently unknown.

Following the guidelines and consensus recommendations, grade  $\geq 2$  CIP requires pharmacological interventions (121-123). A large proportion of the data on pharmacological interventions of grade  $\geq 2$  CIP originate from retrospective studies. Among CIP patients receiving first-line steroid therapy, the efficiency is 56-100% (Table III), Stroud *et al* (124) attempted to treat grade 3-4 CIP with an IL-6R inhibitor (tocilizumab) on the basis of corticosteroid therapy, and 11 of the 12 patients with grade 3-4 CIP exhibited improvements. Commonly used second-line drugs include TNF $\alpha$  inhibitors (Infliximab), mycophenolate mofetil, cyclophosphamide, and intravenous immunoglobulins (Table III) (124-129). Nintedanib has also shown promise in improving CIP (130). IL-1 inhibitors (anakinra and canakinumab), IL-17 inhibitors (ixekizumab, brodalumab, and secukinumab), integrin-4 inhibitors (natalizumab), IL-23 and IL-12 inhibitors (ustekinumab), and anti-B cell antibodies (rituximab and obinutuzumab) have been used to improve irAEs (71,121-123), but their efficacy in CIP remains unknown.

In addition to the applications of steroid hormones, immunosuppressants, and cytokine antagonists to treat irAEs, other strategies to reduce irAEs have also attracted attention. A meta-analysis assessing 14 RCTs suggested that atezolizumab may reduce the incidence of grade  $\geq 3$  CIP compared with other immune-based schedules (131). IL-6 blockade combined with ICIs can alleviate ICI-induced experimental autoimmune encephalomyelitis (132). Thymosin  $\alpha 1$  combined with anti-CTLA-4 antibodies can significantly

Table III. Pharmacological interventions for grade  $\geq 2$  CIP in retrospective studies.

First author, year	Treatment line number	Medications for Treatment	Target/mechanism	Enrollment <sup>a</sup>	Efficacy	Adverse events	(Refs.)
Karayama <i>et al</i> , 2023	First line	Corticosteroids	Immune cells and inflammatory cytokines	56	The pneumonitis control <sup>b</sup> rate at 6 weeks was 91.1%	The most frequent adverse event was hyperglycemia, followed by insomnia, infection, adrenal dysfunction, pneumothorax, and constipation	(125)
Wang <i>et al</i> , 2021				34	All patients achieved clinical remission <sup>c</sup>	Infectious pneumonias	(40)
Suresh <i>et al</i> , 2018				38	56% of patients improved/ completely resolved	Not described	(34)
Naidoo <i>et al</i> , 2017				26	76.9% of patients improved/ completely resolved	Infections	(6)
Stroud <i>et al</i> , 2019		Corticosteroids+ tocilizumab	Immune cells, inflammatory cytokines, and IL-6R	12	11 patients improved	Not described	(124)
Luo <i>et al</i> , 2021	Second line	Infliximab	TNF- $\alpha$	6	The rate of improvement was 50% at 90 days	Not described	(126)
Balaji <i>et al</i> , 2021				2	Not alive	Parainfluenza pneumonia	(127)
Beattie <i>et al</i> , 2021		Infliximab/adalimumab+ mycophenolate mofetil/ cyclophosphamide	TNF- $\alpha$ , inosine monophosphate dehydrogenase/ Alkylating agent	20	Five and twelve patients obtained durable improvement <sup>d</sup> and transient improvement <sup>e</sup> , respectively	Infections	(128)
Beattie <i>et al</i> , 2021		Mycophenolate mofetil	Inosine monophosphate dehydrogenase	6	5 and 1 patients achieved durable improvement and transient improvement, respectively	Infections	(128)
Camard <i>et al</i> , 2022		Cyclophosphamide	Alkylating agent	4	The rate of improvement was 50%	No	(129)
Balaji <i>et al</i> , 2021		Intravenous immunoglobulins	Immune cells, pathogenic autoantibodies, and inflammatory cytokines	7	The rate of improvement was 29%	Herpes zoster	(127)

<sup>a</sup>Enrollment, patients had grade  $\geq 2$  CIP; <sup>b</sup>pneumonitis control, the CIP of patients improved/was resolved; <sup>c</sup>clinical remission, resolution of symptoms or hospital discharge within 7 days; <sup>d</sup>durable improvement, with follow-up of  $\geq 8$  weeks past initial dosing of additional immune modulator; <sup>e</sup>transient improvement, pneumonitis relapse after initial benefit or inadequate follow-up. CIP, checkpoint inhibitor pneumonitis; IL, interleukin; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

reduce the gastrointestinal toxicity induced by anti-CTLA-4 antibodies (133). However, the results of the above two studies are based on animal experiments and have not been confirmed in RCTs.

Following steroid treatment, most patients exhibit improvement. However, ~14% (6/44) of CIP patients still have persistent or worsening pneumonia during steroid reduction, and chronic CIP requires  $\geq 12$  weeks of immunosuppressive therapy (53). Lung cancer patients with CIP have a better maximal tumor shrinkage rate (25.5 vs. 0.0%,  $P=0.014$ ) (38), better objective response rate (61.90 vs. 29.91%), and better PFS (45.80 vs. 21.15 weeks) compared with those without CIP (28). Ono *et al* (26) found that patients with CIP had a longer OS compared with patients without CIP (27.4 vs. 14.8 months). However, the common feature of these studies was the predominance of grade 1-2 CIP and the use of close monitoring. Lung cancer patients with grade  $\geq 3$  CIP have a markedly shorter OS (3.7 vs. 22.1 months,  $P<0.001$ ) (74). The grade  $\geq 3$  CIP-related mortality was 22.7-28.1% in NSCLC (29,42), and patients with grade  $\geq 3$  CIP had a significantly shorter PFS (1.0 vs. 3.5 months) and OS (3.0 vs. 12.7 months) (42). In conclusion, grade 1-2 CIP may be used to predict the effectiveness of an ICI treatment. In contrast, patients with grade  $\geq 3$  CIP may exhibit a reduced response to ICI and shortened survival; thus, assisting in the evaluation of the predictive prognosis of NSCLC patients receiving ICI treatment. However, these findings require further confirmation via randomized and prospective trials.

## 7. Conclusions and future perspectives

ICIs serve as a better treatment option for NSCLC; however, additional attention should be focused on the resulting irAEs, especially CIP. The real-world incidence of CIP is higher than in randomized clinical trials. CIP is commonly seen early in ICI treatment, especially within the first 6 months of initiation of ICIs. The clinical and imaging manifestations of CIP lack specificity, complicating the diagnosis. HRCT may be a promising method in the imaging diagnosis, evaluation, and follow-up of CIP since it can better reflect pulmonary interstitial changes.

Excessive activation and amplification of CTL, Th cells, downregulation of Tregs, and over-secretion of pro-inflammatory cytokines remain the dominant mechanisms underlying the pathophysiology of CIP. The dysregulation of innate immune cells, such as increased levels of inflammatory monocytes, DCs, neutrophils and M1 polarization of macrophages, increased IL-10 and IL-35, and a decrease in the eosinophil levels may underlie the onset and progression of CIP. Nevertheless, several of the above mechanistic findings are based on retrospective studies. It is, therefore, necessary to obtain lung biopsies from CIP patients, especially patients with grade  $\geq 3$  CIP for assessment. Before ICI administration and during the process of CIP, analyzing the components and changes of BALF may provide more evidence of the molecular mechanisms underlying the development of CIP and other pulmonary toxicities. Furthermore, autoantibodies and microorganisms offer novel research avenues.

Although contested, several factors may facilitate the onset of CIP, such as previous ILD, COPD, asthma, radiotherapy, chemotherapy, EGFR-TKI therapy, PD-1 blockers, first-line

application of ICIs, and combined immunotherapy. First-line ICIs plus chemotherapy may reduce the occurrence of CIP. Additional trials are required to further assess the risk factors associated with CIP. With a deeper understanding of CIP, a predictive model may be established to promote the early detection, diagnosis, and treatment of CIP and screen the optimal population for ICI treatment.

Currently, the treatment of grade  $\geq 2$  CIP remains steroid hormone therapy. Despite concerns regarding the toxic effects and the potential to promote tumor progression, cytokine blockers are promising therapeutic agents. The control rate of CIP may be further upgraded by enhancing the targeting of cytokine blockers, reducing their toxicity, and optimizing their combination with steroid hormones. Multi-center, large samples, and interdisciplinary research are imperative to achieve this goal.

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## Authors' contributions

All authors contributed to the study conception and design. XH, JR and QX prepared the manuscript, and collected and assembled the data. XH, RL, DD, JR, JT, XS and JY performed the data analysis and interpretation. XH drafted the manuscript. All authors revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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