

Immune Checkpoint Immunotherapy for Non-Small Cell Lung Cancer

Benefits and Pulmonary Toxicities



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Immune checkpoint inhibitors (ICIs) are newer, immunotherapy-based drugs that have been shown to improve survival in advanced non-small cell lung cancer (NSCLC). Unlike traditional chemotherapeutic agents, ICIs work by boosting the body's natural tumor killing response. However, this unique mechanism of action has also led to the recognition of class-specific side effects. Labeled immune-related adverse events, these toxicities can affect multiple organ systems including the lungs. Immune-mediated lung injury because of ICI use, termed checkpoint inhibitor pneumonitis (CIP), occurs in about 3% to 5% of patients receiving ICIs; however, the real-world incidence of this entity may be higher, especially now that ICIs are being used in nonclinical trial settings. In this review, we briefly introduce the biology of ICIs and the indications for ICI use in NSCLC and then discuss the epidemiology and clinical and radiologic manifestations of CIP. Next, we discuss management strategies for CIP, including the current consensus on management of steroid-refractory CIP. Given the nascent nature of this field, we highlight areas of uncertainty and emerging research questions in the burgeoning field of checkpoint inhibitor pulmonary toxicity.

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Non-small cell lung cancer (NSCLC) is a prevalent disease with high mortality and poor response to traditional cytotoxic therapy. Until recently, the medical management recommended for most patients with advanced stage NSCLC has been limited to combination chemotherapy regimens, which confer a progression-free survival (PFS) of 4 to 6 months and overall survival (OS) of approximately 12 to 18 months.^{1,2} Increases in PFS and OS have

been modestly improved with newer agents, including antiangiogenic therapies such as bevacizumab,³ and with addition of targeted chemotherapy based on the presence of oncogenic-driving mutations.⁴ However, in the last few years, immunotherapeutic agents that target immune checkpoint pathways have shown great promise in clinical trials and have been rapidly incorporated into the standard management of advanced stage NSCLC.⁵

ABBREVIATIONS: AIP = acute interstitial pneumonia; APC = antigen-presenting cell; CIP = checkpoint inhibitor pneumonitis; CTLA-4 = cytotoxic T-lymphocyte antigen-4; HP = hypersensitivity pneumonitis; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; IVIG = IV immunoglobulin; NSCLC = non-small cell lung cancer; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; OS = overall survival; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; PD-L2 = programmed death ligand-2; PFS = progression-free survival

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Immune checkpoints are surface proteins on T cells and other immune cells that act as negative regulators of immune activation by various antigens, including tumor antigens. Immune checkpoint inhibitors (ICIs) are a class of immunotherapeutic agents that harness the intrinsic immune response against tumor antigens by removing the brake on T-cell activation by antigen-presenting cells (APCs). However, by the same process, these agents may also promote T-cell attack on self-antigens, which clinically manifests as a set of unique toxicities labeled immune-related adverse events (irAEs). The first checkpoint to be discovered was CTLA-4, and the ICI developed to target CTLA-4, ipilimumab, demonstrated survival benefit in melanoma.⁶ Such ICI-mediated activation of antitumor activity has also shown great promise in other tumor types as well; for instance, treatment with an ICI targeting either CTLA-4 or programmed death-1 (PD-1), another immune checkpoint, resulted in increased OS and PFS in advanced melanoma,⁷⁻⁹ Merkel cell carcinoma,¹⁰ colon cancer with mismatch-repair deficiency,¹¹ Hodgkin lymphoma,¹² and renal cell carcinoma.¹³ In NSCLC, several trials have demonstrated improvement in survival outcomes for patients with NSCLC with progressive disease after traditional chemotherapy,^{14,15} therefore generating interest in the use of ICIs in both early and late stage NSCLC.

Of the many different checkpoint pathways,¹⁶ the PD-1 pathway, composed of the receptor (PD-1) and its reciprocal ligands (programmed death-ligand 1/2 [PD-L1 and PD-L2, respectively]), and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) pathway, have been most intensely studied in NSCLC in recent years. Monoclonal antibodies targeting PD-1 (eg, nivolumab, pembrolizumab), CTLA-4 (ipilimumab), or PD-L1 (eg, durvalumab, atezolizumab, avelumab) have been studied in late phase clinical trials and demonstrated significant improvements in PFS and OS compared with second-line chemotherapy.¹⁷⁻¹⁹ Based on these results, anti-PD-1/PD-L1 therapies are now the preferred second-line therapy for advanced NSCLC^{1,2,18,20} and even as first-line therapy in certain scenarios.

However, along with tumor killing, ICIs can also cause a spectrum of toxicities that may be mediated by their immunologic mechanisms of action (ie, irAEs). Reported toxicities include colitis, hypophysitis, pneumonitis, thyroiditis, inflammatory arthritis, and more.²¹⁻²⁷ The overall incidence of irAEs has been low in clinical trials that evaluated monotherapy with anti-PD-1 and anti-PD-L1 therapies (typically < 5%).

However, there is now a growing recognition that the actual incidence of irAEs may be higher in certain tumor types, patients treated with combination ICIs, and nontrial settings.^{23,28-30}

Checkpoint inhibitor pneumonitis (CIP) that occurs as a result of anti-PD-1/PD-L1 ICIs remains a rare but concerning complication. CIP is defined as the development of dyspnea and/or other respiratory signs/symptoms (including cough and desaturation with exertion) in the presence of new infiltrates on chest imaging and in the absence of new infection (based on expectorated sputum and/or BAL microbiology). The natural history of CIP is different from other irAEs; for instance, compared with immune-related thyroiditis or hepatitis, which tend to be self-limiting illnesses, most cases of CIP (ie, > grade 2) require treatment with high doses of oral or parenteral steroids. In a large retrospective cohort of patients treated with ICIs across tumor types, the overall incidence of CIP was 5%, and 86% of cases improved with corticosteroids.^{29,30} However, in the 14% of patients with CIP who did not improve with steroids, there was little response to additional immunosuppression and high mortality. Less is known about the incidence of CIP, specifically in patients with NSCLC. In NSCLC trials, the incidence of CIP has typically been reported as ranging from 3.5% to 5%.^{20,31,32} However, the incidence of CIP in NSCLC outside of clinical trials is unclear.

Part of the difficulty in diagnosing CIP is the lack of specific clinical or radiographic markers. The clinical symptoms are often nonspecific, and the radiographic appearance of CIP is varied and may mimic tumor progression. Furthermore, the presence of infection may be difficult to exclude, particularly in patients who cannot undergo bronchoscopy because of significant supplemental oxygen requirements. Most patients who are diagnosed with CIP do respond to steroids; however, there are currently no data to guide treatment for steroid-refractory CIP. This difficulty in choosing second-line therapy arises in part from a lack of understanding of the pathobiology of CIP, including an explanation for why some patients develop clinically severe CIP.

In this review, we will summarize the mechanism of action of ICIs and efficacy of ICIs in the treatment of advanced NSCLC; discuss the clinical, radiologic, and pathologic features of CIP; briefly describe the management strategy for CIP in patients with NSCLC; and discuss future directions for the establishment of

evidence-based management strategies for CIP in patients with NSCLC.

ICI Biology

As part of the intrinsic tumor surveillance process,³³ tumor antigens are processed by APCs and present tumor-derived epitopes to T cells (Fig 1, left panel). On recognition of tumor antigens, antigen-specific T cells have the potential to become activated and proliferate. However, there are several requirements for this process to occur efficiently. First, the tumor must be immunogenic enough to present APCs with sufficient quantity (and quality) of tumor antigens. Second, sufficient T cells must recognize the antigens that are presented. Third, as subsequently detailed, after T-cell activation, counterregulatory mechanisms should not prematurely halt the T-cell proliferative response by inducing T-cell exhaustion, a complex process that decreases T-cell immunoreactivity to cancer antigens because of various tumor microenvironment factors, including expression of immune checkpoints on the surface of T cells.

The process of T-cell activation by an APC requires not only the interaction of the major histocompatibility complex containing the tumor antigen (on the APC surface) with its T-cell counterpart, the T-cell receptor (or TCR, present on the T-cell surface), but also the binding of costimulatory APC surface proteins (eg, B7-

1) to a partner receptor on the T-cell surface. Receipt of MHC-TCR and B7-CD28 binding triggers T-cell activation and proliferation. However, natural mechanisms exist to curtail stimulation of T cells via this process. T-cell proteins such as PD-1 or CTLA-4 serve as negative regulators of T-cell activation. These proteins are expressed on the T-cell surface and, when activated, downregulate T-cell activation and proliferation (Fig 1, left panel). This is thought to be a compensatory mechanism under conditions of chronic antigenic stimulation, such as chronic (often viral) infection.^{34,35}

In the specific case of tumor antigen presentation, two distinct checkpoints have been studied and exploited for therapeutic benefit. First, when an APC presents tumor antigens to a T cell, the checkpoint protein CTLA-4 can curtail T-cell activation by competitively binding APC costimulatory ligands. If the T cell does get activated, a second checkpoint can be encountered when the T cell encounters tumor cells and/or other tissues in the target organ that express the ligand for PD-1, PD-L1. Tumors exploit this second checkpoint by overexpressing PD-L1 as a means of evading T-cell mediated tumor killing, in effect halting infiltrating T cells at the tumor edge. However, if PD-1 and/or PD-L1 signaling is inhibited with immunotherapy, T-cell activation can theoretically proceed unencumbered, leading to a renewed attack on the tumor by newly, unexhausted T cells (Fig 1, right panel).

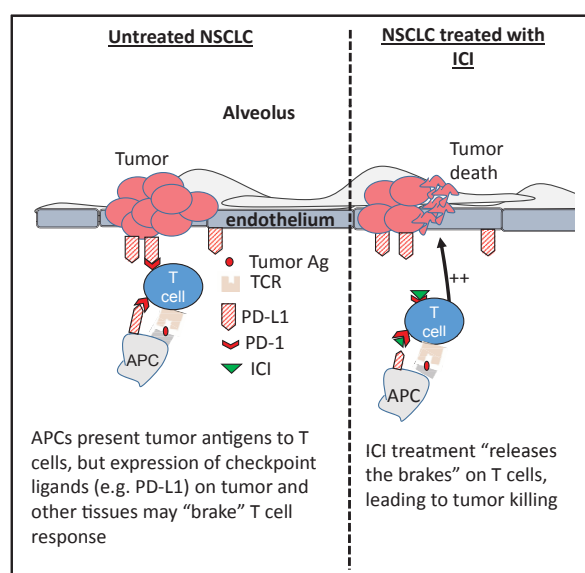


Figure 1 – Schematic showing the actions of checkpoint PD-1 and its ligands PD-L1 in untreated and ICI-treated NSCLC. Ag = antigen; APC = antigen-presenting cell; ICI = immune checkpoint immunotherapy; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; TCR = T-cell receptor.

Efficacy of Anti-PD-1/PD-L1 Therapies

An expanding body of work supports the efficacy of ICIs across a variety of tumor types. In NSCLC, anti-PD-1/PD-L1 ICIs have been studied in the first-line setting (as initial chemotherapeutic agent), maintenance setting (ie, after initial chemoradiation), and second-line setting (ie, after progression while on platinum- or tyrosine kinase inhibitor-based regimens). A detailed analysis of all the trial data supporting ICI use in NSCLC is beyond the scope of this review and is covered elsewhere^{18,36,37}; herein, we briefly review some key studies that support ICI use in commonly seen advanced NSCLC settings.

First-Line Setting

The use of PD-1 ICIs in the first-line setting has also been studied in phase III trials. Pembrolizumab monotherapy compared with standard platinum-doublet chemotherapy in patients with newly diagnosed NSCLC demonstrated improvement in PFS and OS. This study, along with a subset analysis within this study demonstrating safety of coadministration of PD-1

inhibitors with traditional chemotherapy, provided a new standard of care for advanced NSCLC.^{38,39}

Stage III Maintenance Setting

The PD-L1 ICI, durvalumab, was studied in a phase III trial in patients with stage III unresectable NSCLC, after chemoradiation therapy (ie, no evidence of disease progression after chemoradiation). In this study, patients who received durvalumab demonstrated improved PFS compared with placebo (16.8 vs 5.6 months, respectively).⁴⁰

Second-Line Setting

In patients with advanced nonsquamous and squamous NSCLC who progressed on traditional platinum-based regimens, nivolumab improved OS (nonsquamous: 39%-51% at 1 year; squamous: 24%-42% at 1 year) compared with single-agent docetaxel.^{9,10}

In addition to PD-1 ICIs, ICI therapy directed against PD-L1 (atezolizumab) was evaluated in a phase III trial compared with docetaxel, in the second-line setting. Median OS was greater in all patients on atezolizumab, regardless of PD-L1 expression; however, the magnitude of OS benefit was greatest (15 months for the atezolizumab group vs 10 months for the docetaxel group) for the subgroups with detectable tumoral PD-L1 levels.¹⁹

The safety profile of ICIs, including development of irAEs, was reported in the aforementioned studies. However, as subsequently discussed, the true incidence may be higher in the context of ICIs being used increasingly in nonsalvage settings and with greater recognition of CIP as a distinct clinical entity.

Incidence of CIP

The incidence of CIP has been evaluated as part of a constellation of irAEs. In large clinical trials and in meta-analyses, CIP incidence has been reported to be around 3% to 5%.^{29,32} However, higher rates of CIP of approximately 7% to 13%⁴¹⁻⁴³ have been reported in phase I trials of ICIs in NSCLC. Also, in earlier trials, patients' symptoms may have been recorded as dyspnea, cough, or chest pain, but the diagnosis of CIP may not have been made. CIP incidence may also be dependent on the specific type of ICI used; a recent retrospective meta-analysis of ICI use in NSCLC reported a higher incidence of pneumonitis in patients treated with anti-PD-1 therapy compared with patients who received anti-PD-L1 therapy.⁴⁴ The use of combination ICI and/or concurrent therapies may also influence the incidence of

pneumonitis, as suggested by higher reported rates of CIP in a recent phase III trial of the PD-L1 inhibitor durvalumab after chemoradiation for stage III NSCLC.⁴⁰ In summary, the incidence of CIP may be underreported and is likely to change over time with the advent of newer ICIs, newer treatment paradigms for ICI use in NSCLC, and greater recognition of CIP as a distinct clinical entity.

Clinical Presentation of CIP

The clinical presentation of patients with CIP is nonspecific and characterized by dyspnea, cough, fever, chest pain, and progressive decrease in exercise tolerance. The time to onset of symptoms from drug administration can be quite variable; in a large retrospective review of CIP in patients receiving anti-PD-1/PD-L1 ICIs for a variety of tumor types, Naidoo et al³⁰ reported a median time to onset of 2.8 months. In our experience, symptom onset has been extremely variable, with incident cases occurring as early as hours to days after first dose or as late as several months into a course of immunotherapy. In general, review of CIP cases at our center suggests that higher, more severe grades of CIP tend to occur within the first 100 to 200 days of therapy initiation.⁴⁵ In patients with suspected CIP, physical examination is typically fairly unrevealing; patients with more advanced grade pneumonitis may present with crackles on lung auscultation, similar to other interstitial lung diseases. Pneumonitis can occur in isolation without toxicity in other organ systems; therefore, absence of other immune-related toxicities does not help in the determination of CIP.

Given the nonspecific pattern on presentation, vigilant attention to respiratory symptoms is required for early detection of CIP. When suspected, several specific entities should be considered in the differential for CIP (Table 1). Infection remains a foremost consideration. Specifically, in patients who are on high doses of steroids for comorbid conditions (eg, spinal cord compression, intracranial events), pneumocystis pneumonia should be considered. In addition to infection, we have observed several other ICI-specific conditions that may also present with respiratory symptoms. Fulminant myocarditis has been reported with (typically combination) ICIs⁴⁶ and can present with severe hypoxia and bilateral lung infiltrates. In patients who received chest radiation for cancer therapy, radiation pneumonitis can occur in 15% to 20% of cases depending on the dose received, and should be

TABLE 1] Differential Diagnosis of Checkpoint Inhibitor Pneumonitis

Signs/Symptoms/History Elements	DDx
Hypercarbia	ICI-associated myasthenia gravis
SVT, shock, volume overload	ICI-associated myocarditis
Risk factors for TB	ICI-induced reactivation of TB
Recent cytotoxic chemotherapy	DAH, opportunistic infections
Recent high-dose steroid taper (for brain/spine metastasis, etc)	PJP, nocardia, other opportunistic infections
Increase in size of tumor	Pseudoprogression
Recent XRT	Radiation pneumonitis

DAH = diffuse alveolar hemorrhage; DDx = differential diagnosis; ICI = immune checkpoint inhibitor; PJP = pneumocystis jirovecii; SVT = supraventricular tachycardia; XRT = radiation.

considered in the differential diagnosis. Diffuse alveolar hemorrhage is a consideration especially in patients if prior chemotherapy-related thrombocytopenia is present. Data from preclinical TB models⁴⁷ and from immune cells isolated from patients with active TB suggest that the PD-1 pathway plays a critical role in modulating immune responses to *Mycobacterium tuberculosis*.^{48,49} To our knowledge, at least two cases of TB reactivation after PD-1 therapy have been reported.^{50,51} Therefore, TB remains a consideration particularly in patients with TB exposure risk factors. Finally, hypercarbic respiratory failure in a patient on PD-1 therapy should prompt consideration of PD-1-/PD-L1-associated myasthenia gravis.^{26,52}

Ultimately, the diagnosis of CIP is one of exclusion. To this end, in addition to history and examination, we typically perform bronchoscopy with BAL and, in select patients, transbronchial biopsy to rule out infection prior to making the presumptive diagnosis of CIP.

Radiographic Findings

Chest CT scan is the imaging modality of choice for diagnosing CIP. Administration of IV contrast is generally unnecessary unless there is additional concern for pulmonary embolism or other vascular disorders. Although the CT scan appearance of pulmonary drug toxicity has been studied extensively, a variety of imaging patterns can develop depending on the drugs administered.⁵³ Likewise, the CT scan appearance of CIP can vary significantly within the same cohort.

CIP is responsible for a spectrum of lung injuries, from the acute phase (acute interstitial pneumonia [AIP]) to the organizing (organizing pneumonia [OP]) and fibrotic phases (nonspecific interstitial pneumonia [NSIP]).⁵⁴ In addition, changes consistent with hypersensitivity pneumonitis (HP) and nonspecific ground-glass opacities can also be seen. Nishino et al⁴³

reviewed imaging from 20 CIP cases and reported the following rates: 65% OP, 15% NSIP, 10% HP, and 10% AIP/ARDS. The toxicity grades of pneumonitis corresponded to the acuity of lung injury, with the highest grade for AIP/ARDS, followed by OP, and then by NSIP. In another review of 27 CIP cases across multiple tumor types, Naidoo et al³⁰ reported a diverse mix of radiographic patterns: 19% OP, 37% ground-glass opacities, 22% interstitial, 7% HP, and 15% pneumonitis not otherwise specified.

Utility of Bronchoscopy

The utility of bronchoscopy in establishing the diagnosis of CIP is currently unknown. Currently, most patients undergo bronchoscopy to exclude infection. However, whether ICI therapy alone increases risk for atypical infections is actually not known. Insofar as many patients treated with ICIs have other risk factors for atypical (ie, fungal, PCP, viral) infections (such as antecedent steroid or cytotoxic chemotherapy), we generally perform bronchoscopy on most, if not all, patients with suspected CIP. However, studies examining the utility/yield of BAL as a prerequisite for a diagnosis of CIP are needed.

Pathologic Findings

Very little is known about the pathologic findings in CIP lung biopsy specimens. Because most patients undergo transbronchial biopsies, the samples tend to be limited and the patterns observed nonspecific (typically either OP or cellular interstitial pneumonitis). Naidoo et al³⁰ reported the following pathologic patterns on (primarily transbronchial) biopsies in 11 patients with CIP: OP, diffuse alveolar damage, and granulomatous inflammation. In addition, eosinophils were also found in a subset of patients. Delaunay et al⁵⁵ reported biopsy findings in six transbronchial biopsy specimens in a cohort of 64 patients with CIP, and reported presence of

lymphocytes in the tissue specimens. Despite these initial studies, mechanistic studies looking at the specific cell subsets present in the tissue specimens of patients with CIP are currently lacking. Further studies aimed at rigorously examining the cell types present on CIP biopsy specimens are needed.

Management Strategy

To our knowledge, there have been no prospective trials aimed at evaluating optimal treatment strategies for patients with CIP. Current guidelines⁵⁶⁻⁵⁸ and recommendations are therefore based on case reports or small case series. The mainstay of management of CIP is corticosteroid therapy. High doses (typically 1-4 mg/kg) of prednisone/equivalent corticosteroids are initiated once a formal diagnosis has been made. Current guidelines recommend a dose of 1 mg/kg/d of prednisone for lower-grade (ie, grade 2) CIP and 2-4 mg/kg/d for higher-grade (ie, grade 3-4) CIP. Patients who remain without clinical improvement after 48 to 72 hours of corticosteroids are considered steroid-refractory. In this highly morbid population, a variety of second-line immunosuppressive agents have been used, with variable success (as subsequently outlined). However, no clear evidence currently exists to recommend one agent over another for salvage treatment of steroid-refractory CIP.

High-Dose Corticosteroids

As previously mentioned, prompt initiation of high-dose steroids (1-4 mg/kg prednisone/equivalent) has been the mainstay of treatment of CIP. Based on reported irAEs in clinical trials and patient information leaflets,⁵⁹⁻⁶³ the response rates for CIP after initiation of steroids is typically around 70% to 80%. Based largely on consensus opinion, pneumonitis of any grade > 2 is treated with steroids. There have been no trials on steroid dosing regimens, duration, or route of steroid administration. Institutionally, we typically administer prednisone 1 mg/kg and reassess after 3 days of therapy.

Infliximab

Infliximab is a tumor necrosis factor- α inhibitor currently approved for inflammatory bowel disease, rheumatoid arthritis, psoriasis, and ankylosing spondylitis. Several case series and reports of successful treatment of steroid-refractory within clinical trials support the use of infliximab for ICI-related colitis.⁶⁴⁻⁶⁶ Anecdotal evidence suggests that tumor necrosis factor- α inhibitors may also help in steroid refractory cases of pneumonitis; however, their current recommendation

for use in CIP is largely extrapolated from the colitis data, and clear evidence for their efficacy in CIP is lacking.

IV Immunoglobulin

As detailed previously,⁶⁷ IV immunoglobulin (IVIG) has been used for many decades for various infections and inflammatory conditions and is thought to exert its anti-inflammatory effects through a variety of mechanisms, including neutralization of autoantibodies and modulation of T- and B-cell function. It has also been used to treat other irAEs such as ICI-related myasthenia gravis.²⁶ Unlike other immunosuppressive agents, it does not blunt innate and humoral responses to infection; therefore, IVIG represents an attractive option for patients with CIP in whom there is a high clinical suspicion for comorbid infection. Furthermore, in retrospective reviews, because the cause of death in most patients with refractory pneumonitis was primarily sepsis,³⁰ IVIG may be a viable option for second-line management of CIP.

Tocilizumab

Tocilizumab is an IL-6 inhibitor that has been used in the treatment of rheumatologic irAEs, including inflammatory arthritis and sicca syndrome²³ and cytokine release syndrome associated with chimeric antigen receptor T-cell therapy.⁶⁸ A recent report of a single-center experience with drugs for all irAEs including pneumonitis reported a response rate of approximately 80% in patients using a strategy of steroids and tocilizumab for patients refractory to initial steroid treatment.⁶⁹ In light of its known efficacy for rheumatologic irAEs, its use could be considered in a patient presenting with both joint and pulmonary irAEs. Whether tocilizumab should be used as the second-line immunosuppressive drug of choice for patients with irAEs who fail steroids, regardless of specific organ affected, remains to be seen because head-to-head comparison of tocilizumab to other second-line agents has not been performed.

Whether to resume single-agent ICI therapy in patients who develop CIP on double-agent ICI therapy remains under investigation. A recent review of 80 patients who experienced irAEs on dual-agent ICI therapy and were then subsequently challenged with single-agent ICI therapy suggests that, unlike gastrointestinal or ophthalmic irAEs, CIP occurs at a significant rate (33%) on rechallenge.⁷⁰ However, the total number of patients with CIP in this study was small ($n = 4$).

Many questions remain regarding the treatment of CIP. First, the association between the presence of irAE (including CIP) and cancer outcomes in NSCLC is unknown. The concept of adverse events representing positive events indicative of robust antitumor activity dates back to an earlier generation of immunotherapies, such as IL-2.⁷¹ More recently, in patients with melanoma treated with pembrolizumab, development of cutaneous irAEs has been positively correlated with improved cancer outcomes.⁷² Whether such a relationship exists between CIP and NSCLC remains to be seen. Second, the effect of steroid treatment for lower-grade irAEs on cancer outcomes is not known. Third, what role alternative immunosuppressants might play in steroid refractory CIP remains to be determined. Finally, more research into the clinical, radiographic, and biologic characteristics of patients who present with higher-grade CIP, progress to higher-grade CIP, or have higher mortality from CIP is needed to determine whether a subset of patients with CIP should be prophylactically treated. Clinical trials looking at therapies for steroid-refractory pneumonitis and translation studies aiming to better understand the pathobiology of CIP are currently under development.

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