Current Oncology Reports (2020) 22:56
https://doi.org/10.1007/s11912-020-00920-z

LUNG CANCER (H BORGHAEI, SECTION EDITOR)

Checkpoint Inhibitor Pneumonitis: Mechanisms, Characteristics, Management Strategies, and Beyond

Joshua E. Reuss[1,2,3] · Karthik Suresh[4] · Jarushka Naidoo[1,2,3]

Abstract

Purpose of Review Checkpoint inhibitor pneumonitis (CIP) is a toxicity of immune checkpoint blockade (ICB) that can be highly morbid and at times fatal. Here, we review the proposed biologic mechanisms of CIP, epidemiology and risk factors for CIP development, diagnostic work-up and management strategies for CIP, and future directions of CIP research.

Recent Findings CIP incidence appears to be greater in real-world populations and may continue to rise as FDA approvals for ICB continue to expand to multiple malignancies. Multiple retrospective studies and case series have identified potential risk factors for CIP. Several society guidelines have helped to unify the classification of CIP severity and standardize treatment approaches but significant gaps remain, including formal validated diagnostic criteria for CIP.

Summary While significant strides have been made in enhancing the knowledge and management of CIP, ongoing research is needed to continue to advance our understanding of the biologic underpinnings of CIP, as well as optimize diagnostic and management strategies for this potentially devastating toxicity.

Keywords Pneumonitis · Immune-related adverse events · Immunotherapy · Checkpoint blockade · PD-1 · PD-L1 · CTLA-4

Introduction

Novel immune checkpoint blockade (ICB) therapy targeting the programmed death (ligand) 1 (PD-(L)1) receptor complex and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) has fundamentally altered the treatment landscape of advanced cancer. Anti-PD(L)1 and anti-CTLA-4 treatments have now entered the frontline management strategy of multiple advanced malignancies including melanoma, non-small-cell lung cancer (NSCLC), small-cell lung cancer, squamous cell carcinoma of the head and neck, squamous cell skin cancer, basal-cell skin cancer, merkel cell carcinoma, triple negative breast cancer, renal cell cancer, and urothelial cancer. Furthermore, ICB has been approved or is under investigation in both the subsequent line setting in advanced cancers and the (neo)adjuvant setting in localized cancers. These therapies have many advantages over conventional cytotoxic chemotherapy including improved tolerability and exciting durability of response in select patients [1, 2]. But with increased use, there has been heightened awareness of a novel class of toxicities termed immune-related adverse events (irAEs) that can be highly morbid, at times fatal, and pose diagnostic challenges requiring multidisciplinary input.

Pneumonitis is one such irAE that has been associated with fatalities and can pose challenges in both diagnosis and management. Checkpoint inhibitor pneumonitis (CIP) is defined by focal or diffuse inflammation of the lung parenchyma that is typically accompanied by cough, shortness of breath, and hypoxemia though may be asymptomatic [3•]. While early clinical trials and meta-analyses of ICB in advanced cancers suggested a pneumonitis incidence of 3–5% [3•, 4, 5, 6, 7, 8•, 9], more recent studies incorporating real-world populations suggest this could be as high as 13–19% [10, 11•, 12] and may

This article is part of the Topical Collection on *Lung Cancer*

✉ Joshua E. Reuss
Jreuss1@jhmi.edu

✉ Jarushka Naidoo
Jnaidoo1@jhmi.edu

[1] Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[2] Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University, Baltimore, MD, USA

[3] Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, 201 N. Broadway, Viragh Building Box 6, Baltimore, MD 21287, USA

[4] Division of Pulmonary Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Published online: 16 May 2020

be associated with increased mortality [10, 13, 14•]. Furthermore, CIP is the most frequent fatal irAE in anti-PD(L)1 monotherapy trials [15•]. In this comprehensive review, we will survey current studies investigating the biologic underpinnings of CIP. We will discuss the epidemiology of CIP including proposed risk factors for its development, as well as clinical presentation, diagnostic work-up, and guideline-driven management strategies. In addition, we will examine the future directions of CIP research, including novel clinical trial design for CIP treatment and radiomic studies to predict CIP development.

Biologic Mechanisms of CIP

Defining the underlying mechanisms of CIP is an ongoing area of research that has yet to be fully elucidated. That being said, improved knowledge of the mechanistic understanding of ICB, as well as in-depth immunologic assessment of patients who have developed CIP, has resulted in significant strides in this area. Broadly speaking, immune checkpoints such as PD-1 and CTLA-4 act to induce immune tolerance and prevent autoimmunity, but these checkpoints can be effectively adapted by cancer cells to evade immunosurveillance [16]. ICB with anti-PD(L)1 and anti-CTLA4 agents are thus able to exert their effect through robust anti-tumor immune responses. Evidence for this comes from data suggesting that both tumor mutational burden (TMB), defined as the number of non-synonymous genetic mutations within a cancer, and computational predicted neoantigen burden correlate with response to ICB [17]. This supports the hypothesis that tumor-specific neoantigens, generated by non-synonymous genomic mutations, direct anti-tumor immunity through specific cytotoxic T cell responses. It is thus plausible that the manifestation of irAEs acts through stimulation of a similar antigen-specific immune response directed against self-peptides or shared epitopes between tumor and self. In a large-data analysis examining the association between TMB and incidence of iRAEs with PD-1 blockade, Bomze et al. found a positive correlation between the rate of reported irAEs and median TMB across multiple tumor types, with a correlation coefficient suggesting that ~ 50% of the differences in irAE risk across cancer types may be attributed to TMB [18]. Furthermore, in a study of ipilimumab (anti-CTLA4) plus androgen deprivation therapy in metastatic prostate cancer, CD8+ T cell clonal expansion in peripheral blood was found to precede the development of grade 2–3 irAEs [19]. These studies suggest the plausibility of antigen-specific cytotoxic T cell responses playing a role in irAE pathogenesis.

There is evidence to support a similar pathogenic mechanism for CIP. Post-mortem analyses of lung samples and bronchoalveolar lavage fluid (BALF) from patients with clinically significant CIP have demonstrated prominent lymphocytosis enriched with CD8+ T cells [20, 21]. Additionally, by examining BALF from a small cohort of NSCLC patients who did and did not develop CIP, Suresh et al. noted BAL lymphocytosis dominated by central memory T cells in the BALF of CIP patients [22•]. Interestingly, decreased expression of CTLA-4 and PD-L1 was observed on the BALF T-regulatory cells from CIP patients, suggesting both activation of pro-inflammatory immune subsets and attenuation of an immunosuppressive phenotype. These findings are corroborated by several case reports, which identify similar T cell phenotypes in BALF from patients experiencing CIP [23, 24]. In addition, in a small series of patients with CIP, Laubli et al. performed TCR sequencing on tumor-infiltrating lymphocytes and T cells infiltrating inflammatory CIP lesions and noted significant overlap in the T cell repertoire of these sites, but not in the peripheral blood or secondary lymphoid organs [25]. While not conclusive for antigen-specificity, these data highlight the potential of a cytotoxic antigen-directed T cell response driving CIP pathogenesis. If cross-reactivity and immune response to shared epitopes are playing a role in CIP pathogenesis, one might expect an increased incidence of CIP in NSCLC compared to other primary cancers such as RCC or melanoma. Several meta-analyses and single-center studies support this hypothesis [8•, 26–28]. However, other studies have demonstrated no difference in CIP incidence by tumor type [3•, 29, 30].

Several irAEs, such as skin and endocrine adverse events, are believed to occur in part through humoral-mediated autoantibodies [31, 32]. There is emerging evidence that a similar mechanism may occur in CIP as well. Tahir et al. recently utilized a technique called high-throughput serological analysis of recombinant cDNA expression (SEREX) to enable large-scale screening of autoantibodies in ICB-treated patients [33]. In this analysis, the authors identified increased post-treatment plasma levels of anti-CD74 in a discovery cohort of 2 patients with CIP that was subsequently verified in a confirmation cohort of 10 CIP patients in whom a median 1.34-fold increase in anti-CD74 autoantibodies was observed. Intriguingly, overexpression of CD-74 has been observed in viral-mediated interstitial pneumonitis [34] and may suggest a pathogenic nidus for the development of CIP.

Who Is at Risk for Checkpoint Inhibitor Pneumonitis?

With mature clinical trial toxicity data and increased use of ICB worldwide, several risk factors for CIP development have become apparent. The incidence of pneumonitis is higher in patients receiving PD-(L)1 compared with CTLA-4 blockade, with early trials showing an incidence of 3–5% [4, 5] and < 1% [35], respectively. Combination ICB with anti-PD1 and anti-CTLA4 also appears associated with increased risk for pneumonitis [8•, 29, 30, 36]. In addition, several meta-analyses suggest the incidence of pneumonitis may be higher with PD-1 blockade compared with PD-L1 blockade, with an

incidence of ~4% and ~2% respectively [7, 37]. A proposed mechanism for this finding is that PD-L1 inhibitors do not affect the PD-1:PD-L2 interaction, which may play a role in mediating immune tolerance in lung tissue [38]. But while early clinical trials suggested a relatively low incidence of CIP, as use of PD-(L)1 blockade has increased in clinical practice worldwide, studies including real-world populations suggest that CIP incidence might be substantially greater than these early trials suggest. In a retrospective study of 170 NSCLC patients treated with PD-1 blockade at several hospital centers in Japan, the CIP incidence was found to be 16% [10]. In a similar retrospective study of 205 NSCLC patients treated at Johns Hopkins University, a CIP incidence of 19% was observed [11•]. Interestingly, while the incidence of all-grade pneumonitis appears to be higher in real-world populations as opposed to clinical trials, the fraction of significant grade ≥ 3 CIP appears to be relatively consistent across both populations at ~ 40% of those who develop CIP [7, 8•, 10, 11•]. Potential explanations for increased all-grade CIP incidence in real-world populations include heightened awareness of this toxicity, as well as increased co-morbidities and poorer performance status in patients treated outside of clinical trials. Interestingly, both real-world studies demonstrated that CIP development was associated with shorter patient survival [10, 13]. This stands in contrast to multiple analyses suggesting that patients who develop irAEs overall are associated with improved ICB efficacy and survival [39–45]. However, this disparity in observations suggests that irAE type and severity may factor into potential relationships with patient outcomes. Specifically, Tone et al. found that severe grade CIP (≥ grade 3) was associated with decreased PFS and OS in NSCLC patients treated with anti-PD(L)1 therapy [14•]. In addition, in this study, severe CIP was associated with decreased objective response rates (ORR) to ICB, while the occurrence of irAEs excluding CIP was associated with improved ORRs. Further studies are needed to elucidate whether specific irAEs or patient features are associated with improved ICB ORRs and survival.

Multiple retrospective analyses have identified several patient-specific factors and co-morbidities as potential risk factors for CIP. These include baseline interstitial lung disease (ILD)/pulmonary fibrosis [12, 14•, 30, 46], prior thoracic radiotherapy [30, 47], eastern cooperative group (ECOG) functional status ≥ 2 [14•], combination ICB with anti-PD(L)1 and anti-CTLA4 agents [30, 36], treatment combination EGFR-TKI (tyrosine kinase inhibitor) plus ICB therapy [48, 49], and squamous NSCLC histology [11•]. Both ILD/pulmonary fibrosis and prior thoracic radiotherapy affect lung function. This calls into question the possibility that a poorer baseline lung function may confer a higher risk for CIP development. Both co-morbidities are also likely linked to augmented immune interaction in lung tissue. ILD and fibrosis are often the consequence of aberrant immune activation to a particular antigen (i.e., hypersensitivity pneumonitis), and thoracic radiotherapy has been shown to augment immune activation including T cell dynamics and interferon-β release [50]. Further research is needed to reinforce the findings observed in these small retrospective analyses in order to validate these potential CIP risk factors and identify potential mechanisms for CIP development.

How Is Checkpoint Inhibitor Pneumonitis Identified?

Patients with CIP most commonly present clinically with symptoms of cough and dyspnea though may be asymptomatic. In a study of 915 NSCLC and melanoma patients who received anti-PD(L)1 therapy at Memorial Sloan Kettering Cancer Center (MSKCC) and at the Melanoma Institute of Australia, dyspnea occurred in 53% of patients with pneumonitis and cough occurred in 35%, but CIP manifestation was asymptomatic in 33% of cases [3•]. Other observed clinical features include fever, chest pain, hypoxemia, and weakness [3•, 12, 51]. The median time to onset of pneumonitis is 2–3 months though onset can vary significantly, with reported cases ranging from years after therapy initiation, to those that occur during initial therapy infusion [3•, 11•, 30, 52]. In the above study, the median time to onset of pneumonitis was 2.8 months with a range of 9 days to 19.2 months. The median time to CIP development tended to occur earlier with combination as opposed to single-agent ICB with a median of 2.7 and 4.6 months respectively [3•].

The radiographic appearance of CIP can vary considerably [3•, 11•, 12, 51]. In the above study, five radiographic patterns were observed including ground glass opacities (GGO) 37%, hypersensitivity 22%, pneumonitis not otherwise specified (NOS) 22%, cryptogenic organizing pneumonia (COP)–like 19%, and interstitial 7% [3•]. Other studies have demonstrated similar patterns. In a study of 170 patients treated in 10 different trials of nivolumab in which 20 patients developed CIP, the breakdown of observed radiographic patterns was COP-like (65%), non-specific interstitial pneumonia (15%), hypersensitivity (10%), and acute interstitial pneumonia/ARDS (10%) [51]. Of note, the pattern/distribution was mixed and multifocal in 40% of patients and 75% had involvement of all lung lobes. Similarly, in the Johns Hopkins retrospective study cited previously, the majority of patients (66%) did not have a singly characterized radiographic pattern, with 45% of patients having bilateral involvement and 86% having lung involvement away from the peri-tumoral area [11•]. These findings reinforce the need for a high index of suspicion for CIP in the proper clinical context when interpreting imaging studies.

How Is Checkpoint Inhibitor Pneumonitis Diagnosed and Managed?

Since there are no formal validated diagnostic criteria for CIP, the optimal method to diagnose CIP is debated. In addition, the differential diagnosis for CIP can often be complex and include disease progression, infection, thromboembolic event, and other immunotherapy toxicities such as sarcoidosis [53]. Bronchoscopy with BAL and biopsy can be immensely helpful. In the MSKCC study cited above, 11 of 27 patients diagnosed with CIP underwent biopsy with the following histopathologic breakdown: cellular interstitial pneumonitis (36%), organizing pneumonia (27%), diffuse alveolar damage (9%) [3•]. In addition, multiple retrospective reports have identified a lymphocytic pleocytosis in BALF specimens from patients with CIP [21, 22•]. Bronchoscopy with BAL and biopsy can also be helpful in ruling out alternative etiologies such as infection and malignant progression. When possible, multidisciplinary input involving at minimum pulmonology, infectious disease, and radiology is recommended. Some institutions have even established multidisciplinary immunotherapy toxicity management teams, facilitating prompt diagnosis and uniform management recommendations [54]. Furthermore, multiple organizations including the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), Society for Immunotherapy of Cancer (SITC), National Comprehensive Cancer Network (NCCN), and European Respiratory Society (ERS) have published formal guidelines to assist with diagnosis and management of CIP [55–59].

In general, the diagnosis and management plan for CIP depends on the grading of CIP severity (Table 1). For asymptomatic pneumonitis identified strictly by imaging confined to one lobe of lung or < 25% lung parenchyma (grade 1-G1), close observation is recommended. Strong consideration should be made toward holding ICB therapy. Patients should be followed weekly with history and physical exam, in addition to pulse oximetry and repeat chest CT within 4 weeks to assess for resolution/evolution of previously identified changes. ICB may be resumed with close observation with radiographic evidence of improvement or resolution of findings.

If G1 CIP does not improve, patients report symptoms (shortness of breath, cough, chest pain, hypoxemia), pneumonitis involves > 1 lung lobe or 25–50% of lung parenchyma, or instrumental activities of daily living (ADLs) are affected, this is considered G2 pneumonitis. In this scenario, ICB should be held, and a comprehensive diagnostic evaluation (with or without bronchoscopy with BAL) should be considered, with the goal of ruling out infection and malignant progression. A standard infectious evaluation (depending on institutional standard) would typically include nasal viral swab, sputum culture, blood culture, and urine culture. Treatment consists of high-dose corticosteroids with 1–2 mg/kg/d prednisone until symptoms improve to ≤ G1, followed by steroid taper over 4–6 weeks. A decision to resume ICB should be made on a case-by-case basis and take into consideration CIP severity, disease status (progression, stable, response), patient goals, and functional level.

G3 CIP is defined by severe symptoms requiring hospitalization, pneumonitis involving all lobes of lung or > 50% lung parenchyma, or symptoms limiting self-care ADLs, and G4 is defined by life-threatening respiratory compromise. In both instances, ICB should be discontinued and hospitalization is indicated. The infectious and pulmonary work-up outlined above for G2 CIP should be expedited and performed in collaboration with pulmonary and infectious disease specialists. Methylprednisolone at a dose of 1–2 mg/kg/d IV should be initiated with plan to transition to oral prednisone and taper over ≥ 6 weeks after improvement is seen, usually after 48–72 h. Restarting immunotherapy after a resolved G3 event is debated, but in most cases is unlikely to be clinically appropriate.

The role of empiric antibiotics for patients with suspected symptomatic CIP is hotly debated. In those in whom the diagnosis of CIP is questioned, patients may be treated with empiric antibiotics. The effects of this approach on risk for subsequent development of CIP are unknown. In addition, the gut microbiome appears to play a substantial role in ICB efficacy [60] and there is emerging evidence that antibiotic therapy may adversely affect ICB outcomes [61, 62], though prospective studies are needed.

The majority of cases of CIP will improve with this therapeutic approach [3•, 10], though imaging abnormalities may persist beyond clinical recovery [63]. That being said, steroid-refractory CIP is not uncommon. In the retrospective study at Johns Hopkins, 17 of 39 CIP cases did not respond to initial steroid therapy [11•]. In the event of CIP refractory to ≥ 48 h of steroids, guidelines recommend considering infliximab, mycophenolate mofetil, or intravenous immunoglobulin. Tocilizumab (IL-6 receptor antagonistic antibody) has also been used in select cases of steroid-refractory irAEs (including CIP). In a single-center study of 34 patients with steroid-refractory irAEs treated with tocilizumab, 79.4% demonstrated clinical improvement following tocilizumab treatment [64]. That being said, robust data in support of these treatments for steroid-refractory CIP is lacking, and is based largely on small case series and case reports [64–66]. There is currently no evidence-based standard approach for the treatment of steroid-refractory CIP.

Future Directions and Research Needs

In response to the growing clinical phenomenon of CIP, the American Thoracic Society has published a consensus research statement outlining the key CIP research questions with a focus on terminology, biologic mechanisms, risk factors, and identification of at-risk populations, as well as optimization of the

Table 1 Grading, diagnosis and management of checkpoint inhibitor pneumonitis (CIP)[#]

Diagnostic work-up

-History & Physical (H&P), pulse oximetry

-Chest CT w/ contrast (if not already performed)

-Bronchoscopy w/ bronchoalveolar lavage to assess for infection and malignant progression (strongly encouraged for ≥ G2 CIP)

-Infectious work-up (strongly encouraged for ≥ G2 CIP): respiratory viral panel, sputum culture, blood culture, urine culture, others per institutional standard

-Consultation with pulmonology & infectious disease specialists (advised for ≥ G3 CIP)

-Consider pulmonary function tests (PFT)

Grade (G)	Signs/symptoms	Management
G1	Asymptomatic; confined to one lobe of lung or < 25% lung parenchyma	-Consider holding ICB -Consider repeat PFT if baseline exists -Weekly H&P and pulse oximetry -Consider repeat chest CT in 4 weeks or as clinically indicated to assess for resolution/evolution of findings If ICB held, may resume with radiographic improvement/resolution
G2	Symptomatic[*]; involves > 1 lung lobe or 25–50% lung parenchyma; limiting instrumental activities of daily living (ADLs)	-Hold ICB -Consider pulmonology consultation -Consider repeat PFT if baseline exists -Begin oral prednisone 1–2 mg/kg/day and continue until ≤ G1 followed by 4–6 week taper[^] -Consider empiric antibiotics if sufficient clinical suspicion and not fully excluded -Monitor closely with H&P and pulse oximetry every 3–7 days -Consider resuming ICB upon resolution to ≤ G1[**] -If no improvement after 48–72 h, treat as G3
G3	Severe symptoms requiring hospitalization; involves all lung lobes or > 50% lung parenchyma; limiting self-care ADLs; oxygen indicated	-Discontinue ICB permanently[**] -Hospitalize -Strongly recommend consultation with pulmonology & infectious disease, consider PFTs
G4	Life-threatening respiratory compromise	-Begin IV methylprednisolone 1–2 mg/kg/day, transition to oral prednisone once improvement is seen and taper over ≥ 6 weeks[^] -Consider empiric antibiotics if sufficient clinical suspicion and not fully excluded -If no improvement after 48 h of high-dose steroids consider one of follow: • Infliximab 5 mg/kg × 1 (can repeat after 14 days if indicated) • Mycophenolate mofetil 1–1.5 g twice per day • Tocilizumab 4 mg/kg

[#] Adapted from American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines [55, 58]

ICB immune checkpoint blockade

[*] Symptoms include cough, dyspnea, chest pain, hypoxemia, fever, weakness

[^] GI and *Pneumocystis* prophylaxis with proton pump inhibitor and trimethoprim-sulfamethoxazole should be considered for patients receiving ≥ 20 mg prednisone for ≥ 4 weeks or expected steroid courses > 12 weeks

[**] A decision to resume ICB should be made on a case-by-case basis factoring in CIP severity, disease status, patient goals, and functional level

diagnostic evaluation and management strategy for CIP [67•]. Having society-published management guidelines with consistent CIP severity grading has helped to improve recognition of CIP; however, a consensus definition with validated diagnostic criteria has yet to be established. This is of crucial importance, as the bulk of data examining CIP incidence and risk factors is retrospective with widely varying definitions of CIP and poor interrater reliability on CIP diagnosis [68], which makes cross-study comparisons difficult. Implementation of institutional irAE toxicity teams has been useful in this regard [54], and widespread implementation of these teams may improve the consistency in the diagnosis of CIP.

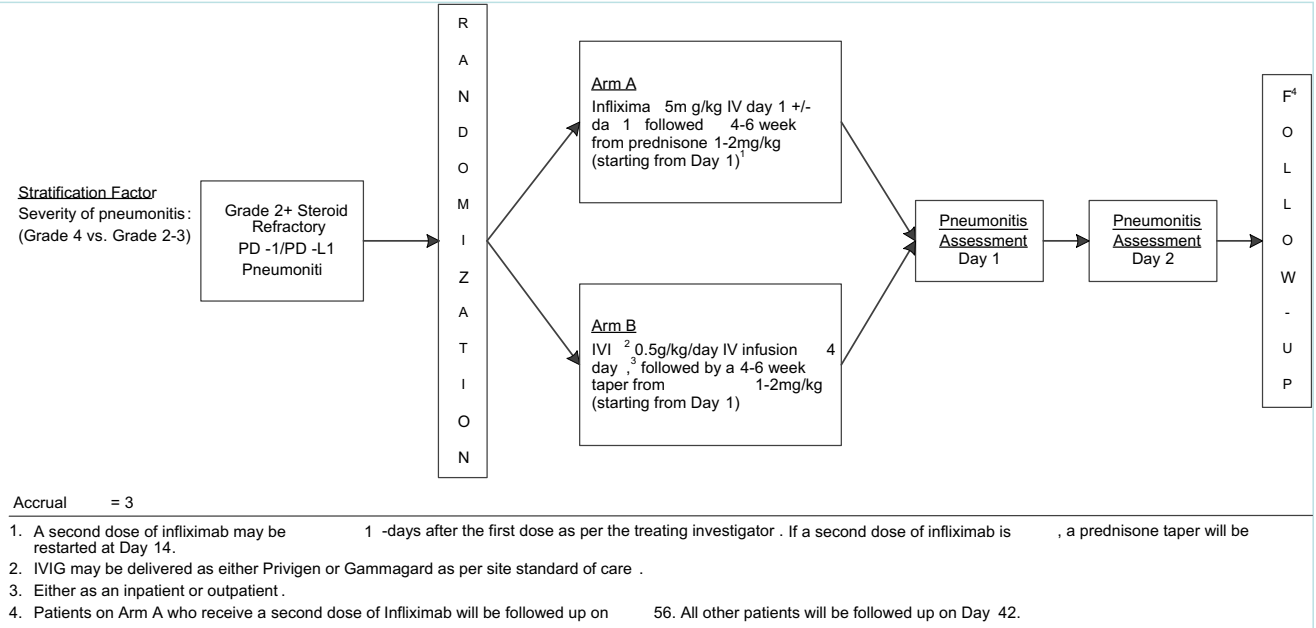

Fig. 1 Proposed ECOG-ACRIN study for optimizing immunosuppression for steroid-refractory anti-PD(L)1 pneumonitis. Patients with ≥G2 steroid-refractory checkpoint inhibitor pneumonitis (CIP) will be randomized to receive infliximab or IVIG at dosing schedules outlined above. The primary endpoint will be pneumonitis response defined as improvement of ≥20% in PaO2/FiO2 ratio assessed on arterial blood gas at baseline (treatment initiation) and 28 days post-treatment. Secondary endpoints include pulmonary function test response, imaging response, and patient-reported outcomes. Biospecimens including blood, bronchoalveolar lavage fluid, and lung tissue will be collected to perform correlative analyses

Enhancing the mechanistic understanding of CIP has been complicated by the fact that a pre-clinical model for CIP has been difficult to establish [69]. Progress is, however, being made in this area. The Lewis lung carcinoma cell line has been used in C57BL/6 mice to study the impact of radiotherapy concurrent with anti-PD1 ICB on lung tissue in tumor bearing mice [70]. In addition, bone marrow–liver–thymus (BLT) immune humanized mice appear to be an encouraging model of irAE, with anti-PD1-treated BLT-humanized strains demonstrating a constellation of irAEs that closely mirrors patterns seen in humans [71]. If a consistent pre-clinical model for CIP can be established, this will help to further our understanding of the biologic underpinnings of CIP. This will prove challenging, however, as a mouse model is unlikely to fully recapitulate the complexities of the human immune response to ICB. BAL studies in human subjects have also helped to further characterize the immune activation seen in CIP [21, 22•, 23, 24], but data to this point has come from small analyses and there are many patient-specific factors that could affect the inflammatory response observed with CIP.

In addition to identifying populations at risk for CIP development, an active area of interest is to identify biomarkers or other metrics that could be used to monitor for CIP development. Multiple cytokines and serum proteins such as

Table 2 Clinical Studies investigating research questions related to checkpoint inhibitor pneumonitis (CIP)

National clinical trial (NCT) number	Clinical question	Location	Study status
NCT04036721	Appropriate corticosteroid duration for CIP (prolonged vs. accelerated taper)	Poland	Not yet recruiting
NCT04169503	Investigate safety of ICB re-challenge following irAEs	France	Recruiting
NCT03984318	Identify predictive markers of irAEs in ICB-treated patients	France	Recruiting
NCT03868046	Evaluate effectiveness of autoantibodies in predicting irAEs	Spain	Recruiting
NCT03305380	Assess utility of radiomics and machine learning to differentiate CIP from other processes	Netherlands	Recruiting
NCT04060407	Single-arm study of CD24Fc with nivolumab & ipilimumab to decrease irAEs	USA	Not yet recruiting
NCT04107311	Prospective analysis of intestinal microbiome and autoimmune panels as predictors of irAEs	Canada	Recruiting
N/A	IVIG vs infliximab for steroid-refractory CIP	USA	Not yet listed

ICB immune checkpoint blockade, *irAE* immune-related adverse event

CXCR2m, IL1ra, and RANTES have been found to coincide with the development of pneumonitis and other irAEs [72, 73]. However, this data comes from small case reports and case series, and needs to be validated in prospective analyses which could prove difficult given the relative low incidence of CIP in ICB-treated patients. Given that poor lung function is a unifying factor connecting several proposed risk factors for CIP, such as prior radiation and baseline ILD, pulmonary function test (PFT) monitoring in CIP is an ongoing area of interest. PFTs are used to monitor for chemotherapy-induced pulmonary toxicity [74]. In addition, PFTs are inexpensive and non-invasive. There is emerging evidence from small retrospective studies that PFTs may be capable of detecting lung function change in ICB-treated patients [75, 76] and multiple guidelines now recommend baseline PFTs prior to ICB initiation [57, 58]. That being said, prospective studies are needed before PFT monitoring can be implemented in a risk management strategy for CIP.

Improving the diagnostic strategy of CIP is incredibly important to focus costly testing and allow for timely initiation of appropriate management. Widespread implementation of multidisciplinary irAE toxicity teams will be extremely important in achieving this goal [54]. However, there are many clinical scenarios, such as private practice and rural settings, where establishing such teams may not be feasible. One active area of research that might help to mitigate this is in radiomics and machine learning to predict CIP development [77]. However, this would still require implementation of an appropriate management strategy.

The ideal treatment approach for steroid-refractory CIP has yet to be determined, with current guideline-recommended strategies based primarily on small case reports and case series. Prospective randomized treatment studies are needed to address this question. A multicenter-randomized study of infliximab vs IVIG for steroid-refractory CIP run through ECOG-ACRIN is in the final stages of preparation (Fig. 1). Other similarly designed studies are needed to assess how other treatments such as mycophenolate mofetil and tocilizumab fit into the treatment strategy for CIP. Multiple additional studies are currently planned or underway to answer other vital CIP-related questions such as ideal steroid duration (NCT04036721), ICB re-challenge (NCT04169503), and predictive biomarkers of irAEs (NCT03984318, NCT03868046) (Table 2). Data from these trials will be instrumental in advancing the diagnostic and management strategies for CIP in ICB-treated patients.

Concluding Remarks

CIP is a highly relevant complication of ICB therapy that can significantly impair quality of life, generate significant costs (both financial and person-hours) associated with diagnostic work-up and management, and prove fatal. Emerging real-world data suggests the incidence of CIP may be higher than previously reported in clinical trials, and this has the potential to increase further as ICB use continues to expand in the treatment of multiple malignancies. While the diagnostic and management approach to CIP has improved with publication of multiple society guidelines, further research is needed to enhance our understanding of the biologic underpinnings, appropriate work-up, and optimal management strategy of this potentially devastating toxicity.

Compliance with Ethical Standards

Conflict of Interest Joshua E. Reuss declares that he has no conflict of interest. Karthik Suresh declares that he has no conflict of interest. Jarushka Naidoo has received research funding from Merck and AstraZeneca; has received compensation from Bristol-Myers Squibb, AstraZeneca, and Roche/Genentech for consulting/advisory board work; and has received honoraria from Bristol-Myers Squibb and AstraZeneca.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. 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(28):2518–27.
2. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2019;381(16):1535–46.
3. • Naidoo J, Wang X, Woo KM, Iyriboz 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(7):709–17 **Seminal retrospective study of ICB-treated NSCLC and melanoma patients that was one of the first publications to provide in-depth characterization of CIP incidence, clinical and radiographic features, pathologic assessment, and management outcomes.**
4. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
5. 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(17):1627–39.
6. 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(2):123–35.
7. Khunger M, Jain P, Rakshit S, Pasupuleti V, Hernandez AV, Stevenson J, et al. Safety and efficacy of PD-1/PD-L1 inhibitors in treatment-naive and chemotherapy-refractory patients with non-small-cell lung cancer: a systematic review and meta-analysis. Clin Lung Cancer. 2018;19(3):e335–48.
8.• 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(12):1607–16 **Comprehensive meta-analysis of ICB clinical trials outlining CIP incidence including severity and stratification by tumor type**.
9. Zhang S, Liang F, Zhu J, Chen Q. Risk of pneumonitis associated with programmed cell death 1 inhibitors in cancer patients: a meta-analysis. Mol Cancer Ther. 2017;16(8):1588–95.
10. Fukihara 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(6):442–450.e4.
11.• 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(12):1930–9 **Single-center analysis of ICB-treated NSCLC patients at Johns Hopkins that outlines potential CIP risk factors, incidence, clinical features, radiographic features, and management outcomes in a real-world population.**
12. 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.
13. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of checkpoint inhibitor pneumonitis on survival in NSCLC patients receiving immune checkpoint immunotherapy. J Thorac Oncol. 2019;14(3):494–502.
14.• 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(10):2006–12 **Single-center analysis of ICB-treated NSCLC patients that highlights potential CIP risk factors and showed that patients with high-grade CIP (≥ G3) had significantly decreased survival compared to those without high-grade CIP.**
15.• 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(12):1721–8 **Comprehensive meta-analysis of World Health Organization database data that details spectrum, timing, and outcomes of fatal ICB-related toxicities.**
16. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3(11):991–8.
17. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science. 2016;351(6280):1463–9.
18. Bomze D, Hasan Ali O, Bate A, Flatz L. Association between immune-related adverse events during anti-PD-1 therapy and tumor mutational burden. JAMA Oncol. 2019. https://doi.org/10.1001/jamaoncol.2019.3221.
19. Subudhi SK, Aparicio A, Gao J, Zurita AJ, Araujo JC, Logothetis CJ, et al. Clonal expansion of CD8 T cells in the systemic circulation precedes development of ipilimumab-induced toxicities. Proc Natl Acad Sci U S A. 2016;113(42):11919–24.
20. Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, et al. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer. 2016;4:13,1 eCollection 2016.
21. Leroy V, Templier C, Faivre JB, Scherpereel A, Fournier C, Mortier L, et al. Pembrolizumab-induced pneumonitis. ERJ Open Res. 2017;3(2). https://doi.org/10.1183/23120541.00081,2016 eCollection 2017 Apr.
22.• 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 **Single-center study at Johns Hopkins that analyzed BAL fluid samples collected from patients with and without CIP. One of the first comparative analyses of the CIP immune landscape that lends insight into the underlying biologic mechanisms of CIP.**
23. Tanaka K, Yanagihara T, Ikematsu Y, Inoue H, Ota K, Kashiwagi E, et al. Detection of identical T cell clones in peritumoral pleural effusion and pneumonitis lesions in a cancer patient during immune-checkpoint blockade. Oncotarget. 2018;9(55):30587–93.
24. Oda K, Kato K, Nakamura M, Jotatsu T, Noguchi S, Kawanami T, et al. Surface marker profiles on lung lymphocytes may predict the mechanism of immune-mediated pneumonitis triggered by tumor-infiltrating lymphocytes in lung cancer patients treated with pembrolizumab. Lung Cancer. 2018;118:171–2.
25. Laubli H, Koelzer VH, Matter MS, Herzig P, Dolder Schlienger B, Wiese MN, et al. The T cell repertoire in tumors overlaps with pulmonary inflammatory lesions in patients treated with checkpoint inhibitors. Oncoimmunology. 2017;7(2):e1386362.
26. Sukari A, Nagasaka M, Alhasan R, Patel D, Wozniak A, Ramchandren R, et al. Cancer site and adverse events induced by immune checkpoint inhibitors: a retrospective analysis of real-life experience at a single institution. Anticancer Res. 2019;39(2):781–90.
27. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol. 2017;28(10):2377–85.
28. 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.
29. Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis. 2016;10(3):183–93.
30. 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(8):4115–20.
31. de Moel EC, Rozeman EA, Kapiteijn EH, Verdegaal EME, Grummels A, Bakker JA, et al. Autoantibody development under treatment with immune-checkpoint inhibitors. Cancer Immunol Res. 2019;7(1):6–11.
32. Ali OH, Bomze D, Ring S, Berner F, Fassler M, Diem S, et al. BP180-specific IgG is associated with skin adverse events, therapy response and overall survival in non-small cell lung cancer patients treated with checkpoint inhibitors. J Am Acad Dermatol. 2020;82(4):854-861. https://doi.org/10.1016/j.jaad.2019.08.045.
33. Tahir SA, Gao J, Miura Y, Blando J, Tidwell RSS, Zhao H, et al. Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities. Proc Natl Acad Sci U S A. 2019;116(44):22246–51.
34. de Souza Costa VH, Baurakiades E, Viola Azevedo ML, Traiano G, Kowal Rosales J, Kunze Larsen KS, et al. Immunohistochemistry analysis of pulmonary infiltrates in necropsy samples of children with non-pandemic lethal respiratory infections (RSV; ADV; PIV1; PIV2; PIV3; FLU A; FLU B). J Clin Virol. 2014;61(2):211–5.

35. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–32.
36. Su Q, Zhu EC, Wu JB, Li T, Hou YL, Wang DY, et al. Risk of pneumonitis and pneumonia associated with immune checkpoint inhibitors for solid tumors: a systematic review and meta-analysis. Front Immunol. 2019;10:108.
37. Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belani CP, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: a systematic analysis of the literature. Cancer. 2018;124(2):271–7.
38. Xiao Y, Yu S, Zhu B, Bedoret D, Bu X, Francisco LM, et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. J Exp Med. 2014;211(5):943–59.
39. 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(11):1358–65.
40. Shafqat H, Gourdin T, Sion A. Immune-related adverse events are linked with improved progression-free survival in patients receiving anti-PD-1/PD-L1 therapy. Semin Oncol. 2018;45(3):156–63.
41. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. Lung Cancer. 2018;115:71–4.
42. Rogado J, Sanchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Levi A, et al. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. Eur J Cancer. 2019;109:21–7.
43. 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(2):479–85.
44. Grangeon M, Tomasini P, Chaleat S, Jeanson A, Souquet-Bressand M, Khobta N, et al. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non-small-cell lung Cancer. Clin Lung Cancer. 2019;20(3):201–7.
45. 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(3):374–8.
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. 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(4):e470–9.
48. 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(8):1112–5.
49. Lisberg A, Cummings A, Goldman JW, Bornazyan K, Reese N, Wang T, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. J Thorac Oncol. 2018;13(8):1138–45.
50. Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Lhuillier C, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. Nat Med. 2018;24(12):1845–51.
51. 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(24):6051–60.
52. Tonk EHJ, van Lindert ASR, JJC V, KPM S. Acute-onset pneumonitis while administering the first dose of durvalumab. Case Rep Oncol. 2019;12(2):621–4.
53. Reuss JE, Kunk PR, Stowman AM, Gru AA, Slingluff CL, Gaughan EM. Sarcoidosis in the setting of combination ipilimumab and nivolumab immunotherapy: a case report & review of the literature. J Immunother Cancer. 2016;4:94,9 eCollection 2016.
54. Naidoo J, Zhang J, Lipson EJ, Forde PM, Suresh K, Moseley KF, et al. A multidisciplinary toxicity team for cancer immunotherapy-related adverse events. J Natl Compr Cancer Netw. 2019;17(6):712–20.
55. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino 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(17):1714–68.
56. Haanen JBAG, 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. 2017;28(suppl_4):iv119–42.
57. Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95 z.
58. National Comprehensive Cancer Network. Management of Immune Checkpoint Inhibitor-Related Toxicities (Version 2.2019) [Internet]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 8 Dec 2019
59. Cadranel J, Canellas A, Matton L, Darrason M, Parrot A, Naccache JM, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. Eur Respir Rev. 2019;28(153). https://doi.org/10.1183/16000617.0058-2019.
60. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97–103.
61. Derosa L, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, Rizvi H, et al. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol. 2018;29(6):1437–44.
62. Pinato DJ, Howlett S, Ottaviani D, Urus H, Patel A, Mineo T, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. JAMA Oncol. 2019. https://doi.org/10.1001/jamaoncol.2019.2785.
63. Johnson DB, Taylor KB, Cohen JV, Ayoubi N, Haugh AM, Wang DY, et al. Anti-PD-1-induced pneumonitis is associated with persistent imaging abnormalities in melanoma patients. Cancer Immunol Res. 2019;7(11):1755–9.
64. Stroud CR, Hegde A, Cherry C, Naqash AR, Sharma N, Addepalli S, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. J Oncol Pharm Pract. 2019;25(3):551–7.
65. Ortega Sanchez G, Jahn K, Savic S, Zippelius A, Laubli H. Treatment of mycophenolate-resistant immune-related organizing pneumonia with infliximab. J Immunother Cancer. 2018;6(1):85–4.
66. Petri CR, Patell R, Batalini F, Rangachari D, Hallowell RW. Severe pulmonary toxicity from immune checkpoint inhibitor treated successfully with intravenous immunoglobulin: case report and review of the literature. Respir Med Case Rep. 2019;27:100834.
67.• Sears CR, Peikert T, Possick JD, Naidoo J, Nishino M, Patel SP, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor-related pneumonitis. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med. 2019;200(6):e31–43 **Consensus statement published by the**

American Thoracic Society that summarizes important findings in CIP research, research gaps, and key research questions to stimulate further investigation.

68. Hsiehchen D, Watters MK, Lu R, Xie Y, Gerber DE. Variation in the assessment of immune-related adverse event occurrence, grade, and timing in patients receiving immune checkpoint inhibitors. JAMA Netw Open. 2019;2(9):e1911519.
69. Liu J, Blake SJ, Smyth MJ, Teng MW. Improved mouse models to assess tumour immunity and irAEs after combination cancer immunotherapies. Clin Transl Immunology. 2014;3(8):e22.
70. Wang F, Luo Y, Tian X, Ma S, Sun Y, You C, et al. Impact of radiotherapy concurrent with anti-PD-1 therapy on the lung tissue of tumor-bearing mice. Radiat Res. 2019;191(3):271–7.
71. Weaver JL, Zadrozny LM, Gabrielson K, Semple KM, Shea KI, Howard KE. BLT-immune humanized mice as a model for Nivolumab-induced immune-mediated adverse events: comparison of the NOG and NOG-EXL strains. Toxicol Sci. 2019;169(1):194–208.
72. Schoenfeld JD, Nishino M, Severgnini M, Manos M, Mak RH, Hodi FS. Pneumonitis resulting from radiation and immune checkpoint blockade illustrates characteristic clinical, radiologic and circulating biomarker features. J Immunother Cancer. 2019;7(1):112–3.
73. Oyanagi J, Koh Y, Sato K, Mori K, Teraoka S, Akamatsu H, et al. Predictive value of serum protein levels in patients with advanced non-small cell lung cancer treated with nivolumab. Lung Cancer. 2019;132:107–13.
74. Lauritsen J, Kier MG, Bandak M, Mortensen MS, Thomsen FB, Mortensen J, et al. Pulmonary function in patients with germ cell cancer treated with bleomycin, etoposide, and cisplatin. J Clin Oncol. 2016;34(13):1492–9.
75. Franzen D, Schad K, Kowalski B, Clarenbach CF, Stupp R, Dummer R, et al. Ipilimumab and early signs of pulmonary toxicity in patients with metastatic melanoma: a prospective observational study. Cancer Immunol Immunother. 2018;67(1):127–34.
76. Reuss J, Suresh K, Psoter K, Forde P, Naidoo J. P1.16-06 early changes in pulmonary function are associated with development of pneumonitis in NSCLC patients receiving immune checkpoint blockade. J Thorac Oncol. 2019;14(10):S587–8.
77. Colen RR, Fujii T, Bilen MA, Kotrotsou A, Abrol S, Hess KR, et al. Radiomics to predict immunotherapy-induced pneumonitis: proof of concept. Investig New Drugs. 2018;36(4):601–7.